UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ENDO PHARMACEUTICALS INC. and GRÜNENTHAL GMBH, Plaintiffs, v. AMNEAL PHARMACEUTICALS, LLC and AMNEAL PHARMACEUTICALS OF NEW YORK, LLC Defendants.	:	12 Civ. 8115 (TPG)
ENDO PHARMACEUTICALS INC. and GRÜNENTHAL GMBH, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. and BARR LABORATORIES, INC. Defendant.	:	12 Civ. 8060 (TPG)
ENDO PHARMACEUTICALS INC. and GRÜNENTHAL GMBH, Plaintiffs, v. IMPAX LABORATORIES, INC. and THORX LABORATORIES, INC. Defendants.	:	12 Civ. 8317 (TPG)
	:	*(captions continued on following pages)*

FINDINGS OF FACT AND CONCLUSIONS OF LAW

ENDO PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. and ACTAVIS SOUTH ATLANTIC LLC, Defendants.	:	12 Civ. 8985 (TPG)
ENDO PHARMACEUTICALS INC. and GRÜNENTHAL GMBH, Plaintiffs, v. IMPAX LABORATORIES, INC., Defendants.	:	13 Civ. 435 (TPG)
ENDO PHARMACEUTICALS INC. and GRÜNENTHAL GMBH, Plaintiffs, v. ACTAVIS INC, ACTAVIS SOUTH ATLANTIC LLC, and WATSON PHARMACEUTICALS, INC., Defendants.	:	13 Civ. 436 (TPG)

ENDO PHARMACEUTICALS INC.,	:	
Plaintiff,	:	
v.	:	13 Civ. 3288 (TPG)
ROXANE LABORATORIES, INC.,	:	
Defendant.	:	
ENDO PHARMACEUTICALS INC.,	:	
Plaintiff,	:	
v.	:	13 Civ. 4343 (TPG) 13 Civ. 8597 (TPG)
SUN PHARMACEUTICAL INDUSTRIES, LTD.	:	
Defendant.	:	

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April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement. Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Grünenthal GmbH (Grünenthal) argue that defendants, all of which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA®ER by selling or seeking approval to sell generic versions of the drug in either crushable or non-crushable formulations. Defendants argue that their generic products, as described in their Abbreviated New Drug Applications ("ANDAs"), do not and will not infringe the patents-in-suit, and that in any event those patents are invalid. Defendants also asserted other statutory and equitable defenses.

There are seven groups of defendants in these cases. Plaintiffs sued the defendants separately, but the cases were tried jointly upon mutual consent. The defendants are: Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, "Amneal"); Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. (collectively, "Teva"); Impax Laboratories, Inc. ("Impax"), ThoRx Laboratories, Inc. ("ThoRx") Actavis Inc., Actavis South Atlantic LLC, and Watson Pharmaceuticals, Inc. (collectively, "Actavis"); Roxane Laboratories, Inc. ("Roxane") and Sun Pharmaceutical Industries ("Sun Pharma.").

There are three patents-in-suit. Endo owns two of the patents, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"). These patents recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing. Grünenthal owns the third patent, United States Patent Number 8,309,060 ("the '060 Patent"), which

describes an invention for drug-tablets so hard that they are difficult to abuse through crushing and snorting, and which also accommodate other barriers to abuse.

The court concludes that defendants' generic products infringe or will infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid. Because each of the defendants infringe the asserted claims of the '122 and '216 Patents, the court enters judgment in Endo's favor and enjoins defendants from selling the generic oxymorphone products described in their ANDAs. With regard to the '060 Patent, the court finds that certain defendants infringe each of the asserted claims, but concludes that defendants have satisfied their burden of showing those claims to be obvious in light of the prior art at the time of the invention. Thus, the asserted claims of the '060 Patent are invalid.

Background Findings of Fact

Endo Pharmaceuticals Inc. was founded in 1997 as a "spinout" from the well-known DuPont Merck Pharmaceutical Company. Trial Tr. at 23:3–5. As a new drug company, Endo had considerable flexibility in deciding which new drug products to develop. *See id.* at 25–27. A number of potential projects were under consideration, including a project to explore developing a certain opioid, oxymorphone, into a controlled-release tablet. *See generally* Project Team Minutes (Feb. 12, 1998) (PTX-0157). Oxymorphone is a semisynthetic opioid created from manipulating morphine, which is derived from poppies. Trial Tr. at 180:7–10. In 1997, Endo sold oxymorphone in intravenous and suppository

formulations. *Id.* at 179:24–25. Both of these formulations provided pain-relief to patients, but were not very profitable. *Id.* at 180:17–18. Thus, Endo was eager to see whether oxymorphone could be developed into a controlled release tablet which patients could take to manage chronic pain at twelve-hour intervals. *Id.* at 406:3–5. Endo believed that if such a product could be developed, it would capture a portion of the then-estimated $650 million market for opioid painkillers. *See* Alliance Committee Meeting Overheads (July 10, 1998) (PTX-0217 at 383).

Oxymorphone had been sold in tablet form between 1959 and 1971 as the branded-drug Numorphan. Trial Tr. at 180:3–4; 1458:7–9. It was pulled from the market in 1971 because of poor sales. Regulatory Background (PTX-0115 at 406). Like the intravenous and suppository formulations of oxymorphone, Numorphan had been an immediate-release drug. Trial Tr. at 1458:11–12. An immediate release drug, when swallowed or otherwise administered, releases almost all of its active ingredient within an hour. Trial Tr. at 176–177; *see also* '122 Patent at 3:20–30. In contrast, a controlled-release drug releases the active ingredient over many hours. *Id.* at 178:12–18. In 1997, when Endo began developing its new product, there had never been a controlled-release formulation of oxymorphone. Briefing Package to FDA (Apr. 6, 2000) (PTX-0223 at 428-31).

Developing oxymorphone into an effective controlled-release formulation presented a number of challenges. First among these was a relative lack of previous research into orally administered oxymorphone's pharmacokinetic

effects, meaning the drug's impact on the human body. *Id.* at 177:3-4. At the time of Endo's development work for oxymorphone there were already two controlled-release opioid painkillers on the market, MS Contin and OxyContin. *Id.* at 204:8–20. Those products were controlled-release formulations of morphine and oxycodone, both of which had been studied extensively in human subjects in their immediate release formulations. *See id.* In contrast, only four studies had been conducted on the effects of orally administered oxymorphone in humans, and each of those had been completed before 1983. *Id.* at 201:9–12; *see also* Briefing Packet (PTX-0223 at 410). Thus, unlike with the development of MS Contin and OxyContin, Endo faced an almost total lack of pharmacokinetic data to use in developing controlled-release oxymorphone. Trial Tr. at 201–02.

This lack of pharmacokinetic data made it difficult for Endo's development team to predict in advance whether oxymorphone would be suitable in a controlled-release form. Oxymorphone in immediate-release form has an exceptionally low bioavailability of only about 10%. *Id.* at 194:9–11. This means that when ingested, 90% of the oxymorphone is metabolized by the liver and only 10% actually enters the bloodstream to provide pain relief. *Id.* This is starkly different from morphine and oxycodone, which exhibit bioavailability of 40% and 60–87% respectively. *See id.* at 2611:6; 2613:21–22. Oxymorphone's unusually low bioavailability in immediate release form raised doubts that it would work in a controlled release setting, where far less of the tablet is dissolved at any given time. *Id.* at 190:8-15.

Endo partnered with another company, Penwest Pharmaceuticals, to

develop oxymorphone into a controlled-release tablet. Trial Tr. at 190. Penwest specialized in the development of pharmaceutical formulations. *Id.* It had invented a technology, called TIMERx, which used natural gums to slow the release of a drug's active ingredient over a period of many hours. *Id.* at 303:12–17. With Penwest as partner, by 1998 Endo had developed tablets of controlled-release oxymorphone hydrochloride (which is oxymorphone in its salt-form). *See* Project Team Minutes (Feb. 12, 1998) (PTX-0157 at 423–24).

Between 1998 and 2001, Endo tested its new formulation in both laboratory settings (*in vitro* testing) and in human subjects and patients (*in vivo* testing). *See* Project Team Minutes (Feb. 12, 1998) (PTX-0157 at 2) (discussing dissolution testing); *see also* Alliance Committee Meeting Minutes (May 2, 2001) (PTX-144) (discussing clinical studies). On October 15, 2001, Endo filed applications with the United States Patent and Trademark Office for patents covering its new controlled release oxymorphone product. *See* United States Patent 3,309,122 at 1 (PTX-0001 at 372); United States Patent 8,329,216 at 1 (PTX-0005 at 463). Shortly thereafter, in December of 2002, Endo filed a New Drug Application ("NDA") with the Food and Drug Administration for the branded drug OPANA®ER. Trial Tr. at 220:2–3.

An NDA is required to obtain regulatory approval to sell branded drugs in the United States. *Id.* at 597:6–11. The new-drug applicant must prove to the FDA, through extensive clinical testing, that the drug is both safe and effective. *Cf.* 21 U.S.C. § 355(b)(1). Moreover, the applicant must inform the FDA of the patents covering the new drug. *See id.* Upon approving the new drug for sale, the

FDA will list all of the patents covering the product in a publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as the "Orange Book."

There is an expedited process when seeking FDA approval of a generic version of a branded drug. The generic manufacturer will file an Abbreviated New Drug Application ("ANDA") with the FDA. This eliminates the need to conduct extensive clinical trials. The generic manufacturer need merely show that the generic drug has the same active ingredient as the branded-drug, and that the two products are bioequivalent. 21 U.S.C. §355 (j). Moreover, the applicant must certify to the FDA that the patents listed in the Orange Book as covering the branded drug do not preclude approval of the generic drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii). One way of doing this is to certify that the patents are invalid, or that the proposed generic product would not infringe those patents. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This type of certification is known as "Paragraph IV" certification. Once a generic manufacturer files a Paragraph IV certification, it must inform the patent holder of the filing. *Id.* This gives the patent holder a period of time in which to bring a lawsuit asserting the patents. *Id.* If the patent holder brings suit, FDA approval of the generic drug will be stayed for 30 months. 21 U.S.C. § 355(j)(5)(B)(iii).

As discussed, Endo filed its New Drug Application for OPANA®ER in December of 2002. Trial Tr. at 220. That NDA would not be approved until 2006, four years later. *Id.* at 185:20–22. In the meantime, Endo continued to perform development work on the OPANA®ER product. *Id.* at 220. Concerned about the

public's abuse of prescription opioids, Endo began exploring ways to make OPANA®ER tamper resistant. *See id.* at 221:10–13. Project team meetings from this time reveal that Endo had considered a number of mechanisms for deterring abuse of OPANA®ER once it was approved by the FDA for sale, including the use of "antagonists," agents in the drug formulation that would block the effect of the opioid if the tablet were tampered with. *Id.*; *see also* PowerPoint Presentation "Opioid Abuse Deterrent (OAD) In-Depth Review" (Dec. 7, 2005) (PTX-0922 at 6). Endo also considered making its tablets difficult to crush, so that the drug would be difficult to sniff or inject. Trial Tr. at 221–22. However, these early efforts were unsuccessful. Trial Tr. at 222.

Things began to change in 2006. In that year, the FDA finally approved Endo's NDA for OPANA®ER. Trial Tr. at 794:18–21. Endo launched the product in August of 2006, and it began to be prescribed by physicians across the country. *See id.* However, Endo remained concerned about the growing abuse of prescription opioids. *Id.* at 796:15–20. Recreational drug abusers would crush OPANA®ER and other opioids and sniff the resulting powder to achieve a euphoric effect. *Id.* Therefore, Endo continued to seek partners for developing a crush-resistant version of the drug. *See* Trial Tr. at 797–98.

Endo found such a partner in Grünenthal GmbH. Grünenthal had developed a process for creating tablet pills with an exceptionally high breaking strength, and also integrating other abuse-deterrent features. Trial Tr. at 1053:1–7. Following the launch of OPANA®ER, Endo sent a delegation to Grünenthal's offices in Germany. *Id.* at 1054:20–21. There, Grünenthal

demonstrated that its technology could be used to create tablets that were exceptionally hard. *Id.* at 155. Moreover, Dr. Bartholomäus, one of the inventors of the technology, showed that the tablets were also effective in releasing the active ingredient of the drug for legitimate use. *Id.* at 1055:22–25. Impressed by this presentation, Endo eventually entered into a license agreement with Grünenthal to use its technology to develop a crush-resistant formulation of the recently-introduced OPANA®ER product. *Id.* at 1056:9–11; *see also* Development, License and Supply Agreement between Grünenthal GmbH and Endo Pharmaceuticals Inc. (Dec. 18, 2007) (PTX-0551).

After its launch in 2006, the original formulation of OPANA®ER became one of Endo's core products. Trial Tr. at 788:16–18. Net sales of the drug were $5 million in 2006, and by 2011 had grown to $384 million. Trial Tr. at 805:20-25. The high sales of OPANA®ER in 2011 ($384 million) marked a dramatic increase from the previous year's sales of $240 million. *See id.* at 806–07. But sales in subsequent years tapered off, amounting to $198 million in 2014. *Id.* at 806:4.

Endo's crush-resistant formulation of OPANA®ER, which it had been developing with Grünenthal, was approved for sale in the United States at the end of 2011. *Id.* at 807:13. Endo launched the new, crush-resistant formulation of OPANA®ER (OPANA®ER CRF) in early 2012. Trial Tr. at 2021:24. Endo then discontinued the sale of the original, non-crush-resistant formulation of OPANA®ER.

In 2012, the Patent and Trademark Office awarded the three patents at

issue in these cases. The '122 and '216 patents cover Endo's invention of a controlled release oxymorphone tablet. The '060 Patent covers Grünenthal's invention of a hard, crush-resistant tablet which also accommodates secondary barriers to abuse.

Defendants are generic drug manufacturers. Each has filed an Abbreviated New Drug Application with the FDA seeking approval to market generic versions of OPANA®ER in its crushable or non-crushable formulations. *See* Trial Tr. at 697:21; 1134; *see also* Summary Chart (PTX-3562) (listing the ANDA numbers for each defendant). Actavis and Sun Pharma sought FDA approval to market both crushable and crush-resistant generic versions of OPANA®ER. Trial Tr. at 599:18-21. Roxane sought approval solely for the crushable version. *See id.* at 600:4–6. Amneal, Teva, Impax, and ThoRx sought approval solely to manufacture crush-resistant generic products. *Id.* at 598:20-23 (referring to PX-4002.80). To date, the FDA has approved the crushable-product ANDAs filed by Actavis and Roxane, but only Actavis has brought its generic product to market. Trial Tr. at 600:3–7.

Between 2012 and 2013, plaintiffs filed lawsuits against each of the defendants for patent infringement. As many as seven patents have been asserted in this case at various times, involving scores of patent claims. However, as trial approached the parties mutually narrowed the number of patents and patent claims asserted. *See, e.g.*, Stipulation and Order Re U.S. Patent 7,851,482 (Doc. #96 in 12-CV-8060). Moreover, on March 17, 2015, the court dismissed one of the patents from the case on collateral estoppel grounds. *See* Order of

March 17, 2015 at 6. Thus, the bench trial involved only the '122, '216, and '060 patents.

Discussion

In an action for patent infringement, it is the plaintiff's burden to prove by a preponderance of the evidence that every limitation of the asserted patent claims is found in the accused device. *Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). "The preponderance of the evidence standard requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence . . . ." *Bosies v. Benedict*, 27 F.3d 539, 542 (Fed. Cir. 1994) (internal quotation marks and citations omitted).

A defendant asserting the invalidity of the patents-in-suit carries a higher burden. The defendant must prove the patents' invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). "Clear and convincing evidence is such evidence that produces 'an abiding conviction that the truth of the factual contentions are highly probable.'" *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (*quoting Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

A. Whether Defendants Infringe the Patents-in-Suit.

Determining patent infringement is a two-step process. First, the court must construe the asserted patent claims. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). Second, the claims as construed must be

compared to the accused device. *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993). The accused device will infringe if it "embodies every limitation of the claim, either literally or by an equivalent." *Id.*

1. Step One: Construing the Asserted Claims.

The first step in the infringement analysis is to construe the asserted patent claims. The purpose of construing the patent claims is not to rewrite the patent, but to simply elaborate on "normally terse claim language" to aid in comprehension thereof. *Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1382 (Fed. Cir. 2005). The words of a patent claim should generally be given their ordinary and customary meaning as would be understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). The primary source of material in determining the claim's meaning is the intrinsic evidence, meaning the patent specification, the patent claims themselves, and the prosecution history of the patent. *Id.* at 1318. The patent specification may show that the inventor had ascribed meanings to certain words that those words do not ordinarily convey, and had acted as his own lexicographer. *Id.* at 136. In such a case, the inventor's definition will govern. *Id.* Likewise, the specification may also disavow the scope of a claim term, and such disavowal will also govern. *Id.* It is only after considering the intrinsic evidence of the claim's meaning that the court may resort to extrinsic evidence, such as dictionaries and treatises, to aid in comprehension of the claim terms. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 n.6 (Fed. Cir. 1996).

Patent claims generally fall into two broad categories: product claims and

method claims. A product claim describes the invention of a physical product, such as a machine or pharmaceutical tablet. A method claim describes a series of steps, or process, constituting the claimed the invention. In construing patent claims, courts "must generally take care to avoid reading [method] limitations into [product] claims . . . because the process by which a product is made is irrelevant to the question of whether that product infringes a pure [product] claim." *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1344 (Fed. Cir. 2008). That being said, some patent claims describe a product by the process used to achieve it. *See Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1291 (Fed. Cir. 2009). Such "product-by-process" claims should be read to require use of the claimed process. *Id.* at 1294.

Claims may be either independent or dependent. 35 U.S.C. § 112(c). An independent claim stands alone. *Id.* In contrast, a dependent claim refers back to a previous independent claim. *Id.* To establish whether a claim is dependent upon another, the court examines if the new claim both refers to an earlier claim and further limits that referent. *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1357 (Fed. Cir. 2007). Significantly, a dependent claim must be construed to incorporate all of the limitations of the independent claim to which it refers. 35 U.S.C. § 112(d).

Pharmaceutical patent claims generally take one of several common forms. *See* Shashank Upadhye, Generic Pharmaceutical Patent and FDA Law §§ 1:9–1:19. Inventors may choose to claim the active pharmaceutical ingredient ("API") itself, meaning the actual molecule at the root of the invention. *Id.* § 1:9.

However, because many APIs cannot be used in their pure form, the inventor will claim the API in its salt-form. *Id.* § 1:10; *see also* Trial Tr. at 1457:6–7. Another type of pharmaceutical patent claim is the "release profile claim." *Id.* § 1:19. A release profile claim recites the amount of an API delivered from a drug at certain intervals. *Id.*

The first step in construing the claims asserted in this case is to define a person of ordinary skill in the art at the time of the inventions. At trial, plaintiffs and defendants provided similar definitions for a person of ordinary skill in the art. Defendants' expert, Dr. Umesh Banakar, testified that such a person would have "at least a master's degree or a doctorate in pharmaceutical sciences with experience in developing formulations, including controlled release formulations. If the individual had a lesser degree of training, such as a bachelor's degree, then he would need several more years of experience in the areas of pharmaceutical formulation development." Trial Tr. at 1502:13–20. Plaintiffs adopted this definition at multiple points during the proceedings, *see, e.g.*, Trial Tr. at 1692:1-3; 1937:2-6, and the court finds that it is a reasonable one. Thus, a person of ordinary skill in the art would possess the above-described qualifications and experience at the time of the inventions.

a. Construing the Asserted Claims of the '122 Patent.

The invention embodied in the '122 Patent is a controlled-release tablet of oxymorphone, effective in providing pain relief over a twelve-hour period. Endo asserts claims 2, 3, 19, and 20 of the '122 Patent against defendants. Claim 1, upon which Claim 2 depends, reads as follows:

> 1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

'122 Patent at 25:50–60.

The intrinsic evidence provides clarity as to how Claim 1 would read to a person of ordinary skill in the art at the time of the invention. First, the claim calls for an "analgesically effective controlled release pharmaceutical composition . . . . in the form of a tablet." '122 Patent Claim 1. A "tablet" is a solid oral dosage form. *Id.* at 3:5. Analgesia is a dulling of the sensation of pain. *See* '122 Patent at 1:15–24. While the patent calls for analgesia, it does not encompass any pain relief regardless of how slight. *See id.* at 4:41–45. Rather, the patent calls for the *effective* dulling of pain. *See id.* at 25:50. The substance must provide pain relief at a level sufficient to treat patients suffering from chronic illnesses. *Id.* at 1:39–40. This means it must treat moderate, severe, or acute chronic pain. *Id.* at 44:43–46. Indeed, the specification defines how much oxymorphone is needed to enter the bloodstream for the dosage form to be considered "effective." *See id.* at 3:41–53. Thus, a person of ordinary skill in the art would read the terms "analgesically effective controlled release pharmaceutical composition . . . . in the form of a tablet" as: a tablet providing pain relief at therapeutically useful levels. *See id.* at 3:4–6.

A "controlled release pharmaceutical composition" is a drug formulation that releases its active ingredient slowly. The specification explains the concept of controlled release drugs by comparison to immediate release drugs. *Id.*at 3:19–33. An immediate release tablet, when dissolved in an environment akin to the human digestive system, releases more than 80% of its active ingredient within 30 minutes. *Id.* at 26. In contrast, a controlled release tablet generally lasts much longer, releasing no more than 80% of its active ingredient in 60 minutes. *See id.* at 3:30–34. Thus, a "controlled release pharmaceutical composition" is a drug formulation that releases its active ingredient slowly over time.

A "dosing interval" refers to length of time between doses of a drug. The specification explains that when a drug is taken by a patient, its effects wear off over time, requiring the patient to take another dose. *Id.* at 1:40–43. The length of time between doses, then, is the dosing interval. *See id.* Claim 1 of the '122 Patent calls for a "twelve hour dosing interval." *Id.* at 25:51. This means that the when a patient takes a dose, it will last for twelve hours before another dose is needed.

Claim 1 requires the tablet to be comprised of "oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet." *Id.* at 25:53–54. Oxymorphone is an opioid analgesic. *Id.* at 1:25. Like many opioids, oxymorphone may be paired with a non-toxic salt for use in medicine. *Id.* at 4:56–62. A "pharmaceutically acceptable salt" of oxymorphone would by oxymorphone hydrochloride, or other salts formed by mixing oxymorphone with acids such as sulfuric acid, nitric acid, and others. *Id.* at

4:58–68. Thus, the patent requires a tablet containing oxymorphone or a salt of oxymorphone as the sole active ingredient.

Claim 1 also requires that the tablet comprise a "controlled release delivery system comprising at least one pharmaceutical excipient." *Id.* at 25:53–56. As discussed, "controlled release" means that a drug's active ingredient releases slowly over time. "Delivery system" refers to the vehicle used to provide the controlled release property. *See id.* at 5:48–62. Such systems include "osmotic pumps"; use of a coating of controlled release film; or use of a "controlled release matrix." *Id.* at 5–6. An "excipient" is a substance other than the active ingredient. *See id.* at 6:1–2. In the context of this claim, it is the excipient (not the oxymorphone) which provides the controlled-release delivery properties of the tablet. *Id.* at 25:54–55.

Claim 1 further provides that "upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C, about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test." *Id.* at 55–60. "In vitro dissolution test" refers to laboratory testing, as opposed to human testing (*in vivo*), of the rate at which a substance dissolves. *See id.* at 3:34–42. "RPM" means revolutions per minute, and pH is a measure of acidity. *Id.* at 464:10-11; 469:1–2. The term "USP Paddle Method" is not defined in the specification. However, a person of ordinary skill in the art would know that "USP" stands for United States Pharmacopeia, a book describing standard formulation methods. Trial Tr. at 467:16-18.

The United States Pharmacopeia describes two dissolution testing methods relevant to this litigation, each of which uses a different dissolution testing apparatus. *See* The National Formulary, The United States Pharmacopeia (1995 ed.) (PTX-0909 at 1792). The first apparatus consists of vessel filled with a fluid. *Id.* at 1791. A metal rod with a basket attached is lowered into the vessel and spun. *Id.* Inside the basket is a tablet. *Id.* As the basket spins in the fluid, the tablet will dissolve. *Id.* This method of dissolution testing, using a basket-apparatus, is known as the "basket method." *See* Figure 1 Below. *Id.* at 1792.

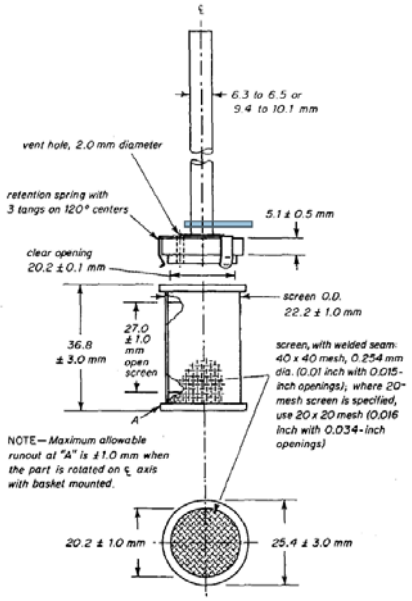


Fig. 1. Basket Stirring Element.

The second apparatus is similar to the first apparatus. However, the second apparatus uses a "paddle," which is formed from a blade, as the stirring element. *Id.* In this method, the tablet is not contained within a basket, but rests at the bottom of the vessel. *Id.* As the paddle spins above the tablet, the tablet will dissolve. *See id.* This method of dissolution testing, using a paddle, is known

as the "paddle method." *See* Figure 2 Below. *Id.*

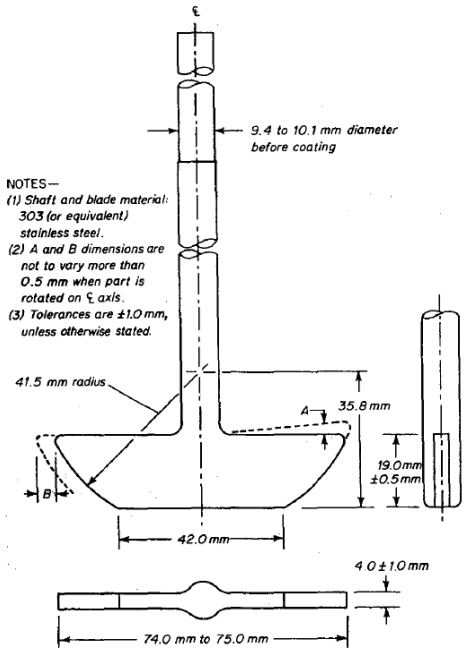


Fig. 2. Paddle Stirring Element.

Thus, a person of ordinary skill in the art would understand the term "USP Paddle Method" as referring to a specific dissolution test described in the United States Pharmacopeia, one that uses a vessel filled with a fluid which is stirred by a blade-shaped paddle.

Finally, the remainder of Claim 1 describes the rate at which the tablet releases the active ingredient using the method described. This language is clear: "about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test."

The release rate is further elaborated in claims 2 and 3 of the '122 Patent. Claim 2 provides that at four hours into the test, "about 45% to about 80%" of the oxymorphone is released. '122 Patent at 25:60–64. Claim 3 provides that at

10 hours into the test, "about 80%" of the oxymorphone is released. *Id.* at 25:65–67.

In sum, Claim 1 of the '122 Patent would, to a person of ordinary skill in the art at the time of the invention, read as follows: "a controlled-release pharmaceutical tablet providing pain relief at therapeutically useful levels for twelve hours, consisting of oxymorphone (or its salt) as the sole active ingredient, and also consisting of a controlled-release delivery system made up of a non-oxymorphone substance that, when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, releases about 15%–50% of the oxymorphone (or its salt) by about an hour into the test." Claim 2 would be read as providing that about 45%–80% of the oxymorphone will be released by about four hours into the test. Finally, Claim 3 provides that about 80% of the oxymorphone will be released by about ten hours into the test.

Endo also asserts Claim 20 of the '122 Patent against defendants. Claim 20 depends from Claim 18. Taken together, the two claims read:

> 18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 1 comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.
>
> 20. The method of claim 18 wherein upon oral administration of the composition the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

'122 Patent at 26:54–58.

The construction of the term "administering" was hotly debated at trial.

Defendants argued that as mere drug manufacturers, they do not actually administer tablet pills to subjects or patients, and thus cannot infringe the method claims of the '122 and '216 patents. *See, e.g.*, Trial Tr. at 611–13. While this argument presents issues of claim construction, it also implicates questions of infringement and indirect infringement, which will be dealt with in subsequent sections of this decision. *See infra* Part A(2)(a)(ii). As matter of claim construction, the meaning of the term "administering" would be readily apparent to a person of ordinary skill in the art upon reading the specification.

The specification uses the term "administering" in two contexts. In the first context, "administering" is used synonymously with the unsupervised "taking" of the drug by patients in order to enjoy long periods of pain relief. *See*, *e.g.*, '122 Patent at 1:39–41; 4:41–48. In the second context, the term "administering" implies a clinical or laboratory setting, wherein an actor, such as a physician or scientist, gives, or more specifically *feeds*, tablet pills to a patient and then observes the results. *See, e.g.*, *id.* at 20:53–55 (beginning on the morning of Day 3, the volunteers were administered a . . . tablet every 12 hours . . . .). Both of these contexts are relevant to claims 18 and 20 of the '122 Patent. Claim 18 recites "a method of treating pain in a subject in need thereof, the method comprising *administering* to the subject the pharmaceutical composition of claim 1." *Id.* at 26:54–56. A person of ordinary skill in the art would understand the "administering" requirement to mean when the subject *takes* the tablet to treat his or her pain, and also when another actor *feeds* the tablet to the subject to treat his or her pain.

Claim 20 incorporates the method of "administering" the tablets described in claim 18, and then provides that "upon oral administration of the composition the oxymorphone AUC($_{0\text{-}inf}$) is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions." *Id.* at 28:1–5. Consistent with the claim construction above, "oral administration" means a subject's *taking* of the tablet by mouth, or the *feeding* of a tablet to a subject to be taken by mouth.

The term "AUC" means "area under the curve," and is a way to measure the concentration of a drug in the bloodstream for a stated period of time, as signified by the subscript within the parenthesis. *See id.* at 11:36–40. Thus, AUC($_{0\text{-}inf}$) means "area under the curve," or concentration of drug in the blood, from zero hours to infinity. *Id.* at 11:40–43. The terms "fed" and "fasted" refer to whether a person has eaten or not. *See id.* at 13:67–14:1 (describing that for a particular study, "fed" patients were those who had eaten a high-fat breakfast). Putting the above constructions together, Claim 20 of the '122 Patent reads as follows: "A method of treating pain in which the subject, upon taking or being fed the tablet orally, exhibits total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach."

The final asserted claim of the '122 Patent is Claim 19. Claim 19 reads as follows:

> 19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt

> thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

'122 Patent at 26:59–27:7. Most of Claim 19 simply restates limitations already recited in claims 1, 2, and 3 of the '122 Patent. Claim 19 differs, however, in that it provides that the controlled release delivering system comprises "a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid." *Id.* at 26:63–65. "Hydrophilic" is not defined in the specification, but a person of ordinary skill in the art would understand it to mean "water-loving," or something that absorbs water. Trial Tr. at 1475:13-15. Upon exposure to gastrointestinal fluid, the water-absorbing material forms a gel which releases oxymorphone slowly. *See* '122 Patent at 6:48–55. In sum, Claim 19 would read the same way as claims 1, 2, and 3 of the '122 Patent, but recites the additional limitation that the controlled release delivery system be comprised of a hydrophilic substance which forms a gel upon exposure to gastrointestinal fluid.

b. Construing the Asserted Claims of the '216 Patent.

The '216 Patent is similar to the '122 Patent, and in fact contains the exact same specification. Consequently, where the two patents share certain language, a person of ordinary skill in the art would interpret that language the same way for both patents. Moreover, many of the asserted claims of the '216 Patent are

repetitive, and repeat the same limitations in different combinations. For these reasons, the court will construe terminology appearing in the '216 Patent claims in the first instance, but where terminology has already been construed, will generally apply the earlier construction. In all, Endo asserts sixteen claims from the '216 Patent, claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82. Those claims, as well as seven independent claims incorporated therein by reference (claims 21, 38, 49, 55, 66, 72, and 77), are construed below.

Claim 1 of the '216 Patent reads as follows:

> 1. An oral controlled release oxymorphone formulation, comprising:
>
> a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
>
> b. a hydrophilic material,
>
> wherein upon oral administration of the formulation to a subject in need of an analgesic effect:
>
> (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
>
> (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
>
> (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
>
> (iv) the duration of the analgesic effect is through at least about 12 hours after administration; and
>
> (v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

'216 Patent at 26:35–55. A person of ordinary skill in the art would understand parts (a) and (b) of the claim as describing a formulation of oxymorphone or its salt combined with a hydrophilic substance. When that formulation is taken by or fed to a subject in need of pain relief, it will produce the effects described in subparts (i) thorough (v).

Subpart (i) states that the formulation "provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone." '216 Patent at 26:42–43. "Blood plasma level" refers to the amount of a substance in the bloodstream. *Cf. id.* at 2:8–14. 6-OH oxymorphone has a technical definition as "the analog of oxymorphone having an alcohol (hydroxy) moiety that replaces the carb oxy moiety found on oxymorphone at the 6-position." *Id.* at 2:65-3:2. While this is the definition a person of ordinary skill in the art would apply, it may be helpful to the reader to explain what 6-OH oxymorphone is in plain terms. At trial, a number of experts explained that 6-OH (or "six-hydroxy") oxymorphone is a byproduct produced when oxymorphone is metabolized in the human liver. *See, e.g.*, Trial Tr. at 592:2–6. This byproduct, known as a "metabolite," will have a measurable presence in the bloodstream. *See id.* at 592–93. Thus, subpart (i) of Claim 1 of the '216 Patent simply means that the formulation will provide detectable levels of the metabolite 6-hydroxy-oxymorphone and oxymorphone in the bloodstream.

Subparts (ii) through (v) of the claim define what those levels will be. Subpart (ii) explains that the blood levels of 6-hydroxy-oxymorphone and oxymorphone will "peak" within about 1 to about 8 hours after administration. '216 Patent at 26:44–46. At trial, there was some dispute among the experts as to what the term "peak" meant. *See* Trial Tr. at 1575:7–10. But such debate is academic in light of the specification. The specification refers to "peaks" of curves as drawn on charts. *See* '216 Patent at 12:58–67. Upon looking at the charts, one of ordinary skill in the art would immediately recognize a "peak" as occurring

where blood concentration reaches a high-point before declining. *See* Figure 5 below.

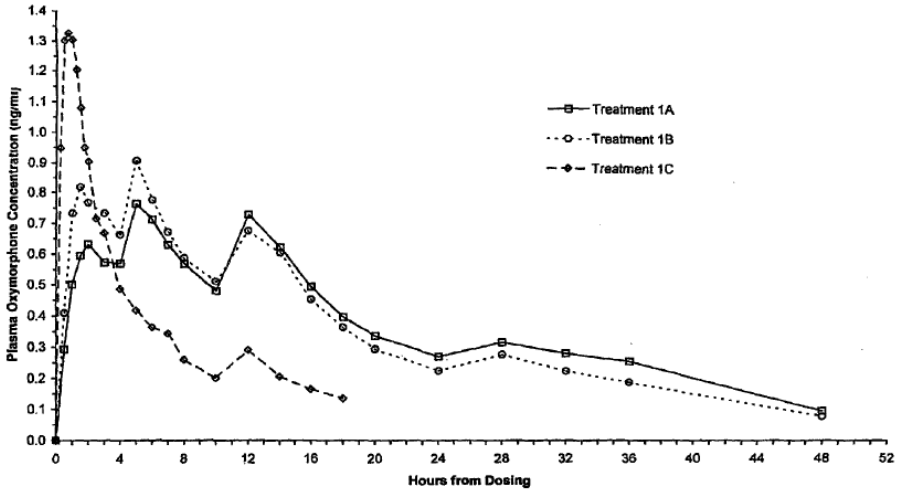


Figure 5

'216 Patent at "Sheet 5."

Subpart (iii) provides that "the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5." '216 Patent at 26:47–51. This means that upon measuring the total amount of 6-hydroxy-oxymorphone (the metabolite) in the bloodstream over time, and comparing that amount to the total amount of oxymorphone in the bloodstream over time, there will be between half to 50% more 6-hydroxy-oxymorphone in the bloodstream than oxymorphone in the bloodstream. *Cf. id.* at 3:51-53.

The final subparts of Claim 1 are clear. Subpart (iv) provides that the pain killing effect of the formulation will last about twelve hours; and subpart (v) provides that the blood plasma level of oxymorphone will exhibit two or three

peaks, or high-points, within twelve hours of administration. *See id.* at 26:52–54.

Claim 21 of the '216 Patent is similar to claims asserted in the '122 Patent. Claim 21 provides:

> 21. A pharmaceutical tablet prepared by:
> a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and
> b. forming the tablet,
> wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

'216 Patent at 28:10–22.

A person of ordinary skill in the art would understand part (a) of Claim 21 as describing a tablet made by mixing oxymorphone or its salt with a substance to slow release of the active ingredient. Part (b) calls for "forming" the tablet. "Forming" is not explicitly defined in the specification, but is used in contexts implying a meaning synonymous with "making." Indeed, the specification states that the invention "includes a method of making an oxymorphone controlled release . . . form . . . which comprises mixing the particles of oxymorphone . . . with granules comprising the controlled release delivery system." *Id.* at 4:52-57. It then says that a preferred means of doing this is to "directly compress the mixture to form tablets." *Id.* This latter step, compression, is embodied in Claim 13. *See id.* at 27:38–39. But as used in Claim 21, the phrase "forming the tablet" simply means "making the tablet."

The remainder of Claim 21 would be understood as requiring that when

tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the tablet releases about 15%–50% of the oxymorphone (or its salt) by about an hour into the test, and that when taken by or fed to a human subject, the tablet will provide pain relief for 12 to 24 hours. *See id.* at 28:15–23.

Claim 22 depends from Claim 21, and further describes the rate at which the dosage form will release the active ingredient over time. *Id.* at 28:23–27. The tablet will release about 45% to about 85% of the oxymorphone or its salt at about 4 hours in the test, and will release about 80% of the oxymorphone at about 10 hours into the test. *Id.*

Claim 38 is a method claim, and reads as follows:

> 38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:
>
> (a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and
>
> (b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

'216 Patent at 29:49–30:5.

Parts (a) and (b) of Claim 38 require the "providing" and "administering" of the dosage form to a person in need of acute or chronic pain relief. *Id.* Because the terms "providing" and "administering" are used separately in Claim 38, those terms, as a matter of construction, have distinct meanings. It has already been established that "administering" involves either the *taking* of a dosage form by the subject, *see, e.g.*, '216 Patent at 4:42–43 (discussing the taking of two or three doses daily to manage pain), or the *feeding* of a dosage form to the subject by another actor. *Id.* at 5:13–14. Such an actor might be a scientist who *feeds* tablets to subjects in conducting a study. *See, e.g.*, '216 Patent at 5:9–18.

Because "administration" involves the taking or feeding of the dosage form, it represents a terminal point in the process described in Claim 38. Since this is the termination of the process, then "making" the dosage form marks some distant beginning (although it is not a part of the actual method claim). The specification speaks of "making" the dosage form in terms of actually manufacturing it, or actually mixing oxymorphone or its salt with a controlled release delivery system. *See, e.g.*, '216 Patent at 4:51-58; 28:10–14.

"Providing" the dosage form, then, must come before administering in the method recited in Claim 38. The dosage form must first be made (manufactured), then provided to the subject, and then administered to subject. *Id.* at 29:50–30:1–2. In this context, "providing" is synonymous with "making available." After the dosage form is manufactured, it is made available (provided) to a subject who takes it or has it fed to him by another person. Thus, the court construes the

term "providing" as the "making available" of the dosage form described in the claims.

The remainder of Claim 38 covers familiar ground. The claim requires, in subpart (a), the making available to subjects of a 5mg to 80mg controlled-release dosage form of oxymorphone or its salt, with a release rate "designed to provide"[1] sufficient blood levels to achieve pain relief over a 12 hour period, and that when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the oxymorphone will be released about 15%–50% at about one hour in the test, about 45%–80% at about fours in the test; and at least 80% at about 10 hours into the test. '216 Patent at 29:50–67. Subpart (b) of Claim 38 requires the taking or feeding of a single dose by or to a subject. *Id.* at 30:1–2.

Finally, Claim 38 requires that once the dose is provided and administered, "the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions." "C_{max}" means the maximum observed concentration of a drug in the bloodstream. '216 Patent at 11:44. It measures concentration of the drug at its highest single point, and consequently is different than the measurement of "AUC," or area under the curve, which measures the concentration of the drug in the blood over a stated period of time. *See id.* at 11:40–43. Thus, this portion of the claim would be understood by a person of ordinary skill in the art as meaning "the maximum

[1] The parties agree that "designed to provide" means simply "that provides," and does not require a specific intention. *See* Second Stipulation and Order (Apr. 9, 2015) ¶¶ 1–2.

observed concentration of oxymorphone in the bloodstream is at least 50% percent higher when the dosage form is taken by (or fed to) a subject after having eaten a meal than it would be on an empty stomach."

Claim 40 of the '216 Patent depends from Claim 38, and recites the additional limitation that "the difference in the oxymorphone area under the curve AUC($_{0\text{-}inf}$) between fed and fasted conditions is less than 20%." *Id.* at 30:10–12. As discussed above, this language would be understood by a person of ordinary skill in the art as meaning that, having taken the dosage form, the subject will exhibit total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the dosage form on an empty stomach.

Claim 42 also depends from claim 38, and reads as follows:

> 42. The method of claim 38 wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:
> (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
> (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and
> (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of AUC($_{0\text{-}inf}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

Id. at 30:15–27. A person of ordinary skill in the art would understand part (i) of the claim to require that the dosage form provide detectable levels of 6-hydroxy-oxymorphone (the metabolite) and oxymorphone; and would understand part (ii) to require that the levels of both 6-hydroxy-oxymorphone and oxymorphone "peak," or reach a high-point, within 1 to 8 hours after the dosage form is taken.

Finally, a person of ordinary skill in the art would understand part (iii) to require that the ratio of 6-hydroxy-oxymorphone to oxymorphone in the bloodstream will be between about 0.5 to 1.5.

Claims 49, 50, and 54 of the '216 Patent are composition claims with terms already construed in the preceding paragraphs of this decision. The claims read as follows:

> 49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:
>
> a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and
>
> b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,
>
> wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.
>
> 50. The composition of claim 49 wherein upon oral administration thereof the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.
>
> 54. The composition of claim 49 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

'216 Patent at 30:52–31:26.

Claim 49 would be understood by a person of ordinary skill in the art as

describing a pharmaceutical composition of 5mg to 80mg of oxymorphone or its salt to be taken orally and which provides, in a controlled or "slow" fashion, pain relief at therapeutically useful levels over a twelve hour period. The maximum concentration of oxymorphone in the blood will be at least 50% higher when the dose is taken after eating a meal as opposed to on an empty stomach. The composition would, when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, release about 15% to about 50% of the oxymorphone or its salt at about an hour into the test.

Claim 50 would be understood as stating the additional limitation that the composition of Claim 49, upon being administered, will produce total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach. Finally, Claim 54 would be understood to mean that the composition of Claim 49, upon being tested using the Paddle Method at 50 revolutions per minute and under certain other conditions, would release about 45% to about 80% of the oxymorphone at about 4 hours in the test, and would release about 80% of the oxymorphone or its salt at about 10 hours in the test.

Claim 55, 57, 62, 64, and 66 of the '216 Patent are also composition claims whose terms were construed in the previous sections of this decision. Together, those claims read as follows:

> 55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:
>
> a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period;

and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

57. The composition of claim 55; wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

62. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

64. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

> wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

'216 Patent at 31:27–32:50.

Parts (a) and (b) of Claim 55 are nearly identical to Claim 49, except that part (a) contains the additional language: "a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of *oxymorphone and 6-hydroxy-oxymorphone* over at least 12 hours to provide sustained pain relief over this same period." *Id.* at 31:29–34 (additional language in italics). A person of ordinary skill in the art would understand this language to mean a delivery system that releases the active ingredient slowly over time that provides adequate blood plasma levels of oxymorphone or 6-hydroxy-oxymorphone (the metabolite) over at least 12 hours to provide sustained pain relief over this same period.

The remainder of Claim 55 would be understood to mean that upon testing the composition in the laboratory using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the composition will release about 15% to about 50 of the oxymorphone or its salt at about one hour in the test.

Claim 57 depends from Claim 55, but recites narrower dissolution ranges when the composition is tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature. *See* '216 Patent

at 49–67. The claim provides that the oxymorphone or its salt will be released at the following rates: at least 27% at about 1 hour into the test; at least 40% at about 2 hours into the test; at least 50% at about 3 hours into the test; at least 64% at about 5 hours in the test, at least 70% at about 6 hours in the test, at least 79% at about 8 hours in the test, at least 85% at about 10 hours in the test, and at least 89% at about 12 hours in the test. *Id.* at 31:52–67.

Claims 62 and 64 would be understood as simply restating, in individual fashion, two of the dissolution limitations already recited in Claim 57. *Compare id.* at 32:18–21 and 32:26–29 *with* 31:59–65. Specifically, Claim 62 requires that the composition of Claim 55 release at least 70% of the oxymorphone or its salt at about 6 hours into the test; and Claim 64 requires that the composition of Claim 55 release at least at least 85% of the oxymorphone or its salt at about 10 hours in the test.

Claim 66 is almost identical to Claim 55, except that part (a) of Claim 66 omits the language "of oxymorphone and 6-hydroxy-oxymorphone" contained in part (a) of Claim 55. *See* '216 Patent at 32:37–38. Additionally, Claim 66 provides that: "wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks." *Id.* at 32:48–50. As discussed above, a "peak" would be recognized by a person of ordinary skill in the art as occurring when blood concentration of oxymorphone reaches a high-point before declining. The last clause of Claim 66 would be understood, then, as requiring that blood plasma levels of oxymorphone reach one or more high-points after the composition is taken by or fed to a human

subject.

Claim 71 depends from Claim 66, and provides that the composition be in tablet form, and release about 45% to about 80% of its oxymorphone or its salt at about 4 hours in the test, and at least about 80% of the oxymorphone or its salt at about 10 hours in the test. *See* '216 Patent at 33:8–14.

Claim 72 of the '216 Patent describes a composition of oxymorphone that uses a "controlled release matrix . . . of a gelling agent which forms a gel upon exposure to gastrointestinal fluid." '216 Patent at 33:14–20. Claim 72 reads as follow:

> 72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;
>
> wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

Id. at 33:14–26.

The specification explains that a "controlled release matrix" exists when oxymorphone is paired with a certain type of controlled release delivery system. *Id.* 6:48–51. That delivery system consists of a gelling agent. *Id.* at 6:52. The gelling agent is a hydrophilic material, such as xanthan gum, that gels when exposed to gastrointestinal fluid. *See id.* 6:7:12–15. Because the substance forms a gel upon exposure to gastrointestinal fluid, it releases the active ingredient, or oxymorphone, at a controlled rate rather than all at once. *See id.* at 6:50–53.

Thus, a person of ordinary skill in the art would understand the terms "controlled release matrix . . . comprising . . . a gelling agent" to mean the pairing of oxymorphone or its salt with a controlled release delivery system consisting of a gelling agent, a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid which releases the oxymorphone slowly.

The remainder of Claim 72 as provides that between about 10% to about 75% of the controlled release matrix will consist of the gelling agent. '216 Patent at 33:18–19. Moreover, upon being tested in the laboratory using the Paddle Method at 50 revolutions per minute in media of a certain acidity and temperature, about 15% to about 50% of the oxymorphone or its salt will be released at about 1 hour into the test. *Id.* at 33:20–26.

Claims 73 and 74 of the '216 Patent depend from Claim 72, and provide that the composition of Claim 72 will release about 45% to about 80% of the oxymorphone or its salt at about four hours in the dissolution test; and at least 80% of the oxymorphone or its salt after about 10 hours in the test. *See* '216 Patent at 33:27–37.

Claim 77 is an independent claim that brings together many of the limitations discussed earlier. Claim 77 reads as follows:

> 77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;
>
> wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50rpm in 500ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is

> released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test,
>
> wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

'216 Patent at 33:56–34:18.

Claim 77 would be understood by a person of ordinary skill in the art as reciting a pharmaceutical composition with oxymorphone or its salt as the active ingredient paired with a controlled-release matrix, which is a controlled-release delivery system consisting of about 10% to 75% of a gelling agent, a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid. *See* '216 Patent at 33:56–67. Moreover, Claim 77 would be understood as requiring that the composition, upon being tested in the laboratory using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, will release about 15% to about 50% of the oxymorphone or its salt after about 1 hour in the test, about 45% to about 80% of the oxymorphone or its salt after about 4 hours in the test, and at least 80% of the oxymorphone or its salt after about 10 hours in the test. *Id.* at 34:1–11. Finally, Claim 77 would also be read as providing that upon the composition being taken by or fed to a human subject, the maximum observed concentration (C_{max}) of oxymorphone in the bloodstream will be at least 50% percent higher after having eaten a meal than it would be on

an empty stomach, and the total blood concentration levels of oxymorphone, as measured by area under the curve, will be no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach. *Id.* at 34:11–18.

Claim 78 depends from Claim 77, and thus incorporates all of Claim 77's limitations. However, Claim 78 recites a number of additional limitations already construed for Claim 1. *See* '216 Patent at 26:40–55. To a person of ordinary skill in the art, Claim 78 would be read to mean: the composition of Claim 77 which, when taken by or fed to a subject in need of pain relief, will produce two or three peaks, or high-points, in blood oxymorphone levels within about the first twelve hours. Moreover, part (i) means that the formulation will provide detectable levels of the metabolite 6-hydroxy-oxymorphone and oxymorphone in the bloodstream. Part (ii) explains that the blood levels of 6-hydroxy-oxymorphone and oxymorphone will "peak," or reach a high-point, within about 1 to about 8 hours after administration. Part (iii) means that after the composition is taken, the total amount of 6-hydroxy-oxymorphone (the metabolite) in the bloodstream over time will be between half to 50% more than the total oxymorphone in the bloodstream. Finally, part (iv) provides that the pain relief will last at least twelve hours.

Claims 79 and 80 recite additional dissolution ranges for the composition of Claim 77. '216 Patent at 34:19–43. A person of ordinary skill in the art would understand the claims as providing that the composition of Claim 77 will release about 58% to about 66% of the oxymorphone or its salt after about 4 hours in the test; and will release about 85% to about 96% of the oxymorphone or its salt

after about 10 hours in the test. *id.*

Claim 82 of the '216 Patent is a method claim reading as follows:

> 82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 77 in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

'216 Patent at 34:56–60. A person of ordinary skill in the art would understand the claim as follows: a method of treating pain in a subject in need pain relief, by which the subject is fed or takes the composition described in Claim 77 in sufficient amounts as to provide 5mg to about 80mg of the oxymorphone or its salt to the subject.

c. Construing the Asserted Claims of the '060 Patent.

The '060 Patent is the product of co-plaintiff Grünenthal's efforts to invent a dosage form so hard that it is difficult to abuse by crushing, and which also accommodates secondary barriers to abuse. *See* '060 Patent at 2:26–62. Plaintiffs assert twelve claims of the '060 Patent, claims 1, 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34[2]. Those claims, as well as three independent claims incorporated therein (claims 22, 23, and 28), will be construed in the following paragraphs of this decision.

Claim 1 of the '060 Patent reads as follows:

> 1. An abuse-proofed, thermoformed dosage form comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological measurements, and optionally at least one wax (D), wherein the

[2] Claim 34 is not asserted against Teva.

dosage form exhibits a breaking strength of at least 500 N.

'060 Patent at 21:6–14.

At trial, the parties identified four areas of dispute regarding the construction of Claim 1 of the '060 Patent: (i) whether the term "abuse-proofed" requires a demonstrated elimination of abuse, or merely a reduction in the potential for abuse; (ii) whether the term "thermoformed" involves the subsequent application of heat; (iii) whether "breaking" involves requires separation of the dosage form into two or more pieces; and (iv) whether Claim 9 requires a separate viscosity increasing agent that forms a gel.

i. The Term "Abuse-Proofed" Means a Reduction in the Potential for Abuse.

Claim 1 recites "an abuse-proofed thermoformed dosage form." *Id.* at 21:6–7. At trial, the parties suggested different readings of the term "abuse-proofed." Defendant Actavis argued that the term "abuse-proofed" means that the dosage form must achieve a demonstrated and significant elimination of abuse, and plaintiffs argued that "abuse-proofed" requires merely a reduction in the potential for abuse. *See, e.g.*, Trial Tr. at 1137:7–11; 2151–52.

Plaintiffs' construction of "abuse-proofed" is correct. The '060 Patent certainly aims to combat abuse of opioids, but the specification makes clear that it does not require a demonstrated elimination of abuse. The specification explains that opioids, because of their efficacy in treating pain, "also have abuse potential," meaning they can be "used by abusers to induce a state of . . . euphoria," or a high. '060 Patent at 1:25–32. Abuse is possible when users grind opioid dosage forms in a mortar and sniff the resulting powder, or mix the powder

with water to inject intravenously. *Id.*at 32–49. The purpose of the Grünenthal's invention was to "*complicate* or prevent the pulverization" of dosage forms to prevent abuse "simply by pulverization." *Id.* at 2:5–14. To this end, the Grünenthal patent recites a dosage form of exceptional hardness, so hard that "pulverization . . . is considerably more difficult using conventional means" like a hammer, mortar and pestle, or mallet. *Id.* at 2:227–42. Moreover, the Grünenthal invention accommodates the inclusion of additional barriers to abuse, such as irritants to deter snorting, or the use of a "viscosity-increasing agent" to complicate injection. *Id.* at 6:35–54.

This language does not require a demonstrated reduction of abuse, or even the elimination of the ability to crush the dosage form. Rather, it signifies to a person of ordinary skill in the art that the invention intends to *reduce the potential for abuse*, to make it potentially more difficult. *See id.* at 6:24–34. ("In the event of . . . pulverization . . . achieved by application of extreme force, the dosage forms . . . may . . . contain further agents which *complicate* or prevent abuse." *Id.* at 6:24–34." But this does not require the showing of a demonstrated actual reduction in abuse.

A person of ordinary skill in the art, upon reading the specification, would understand the term "abuse-proofed" as requiring "a reduction in the potential for abuse."

ii. The Term "Thermoformed" Allows for the Subsequent Application of Heat.

At trial, the parties vigorously debated the meaning of the term

"thermoformed." *See, e.g.*, Trial Tr. at 1138:5–9. There is general agreement that "thermoforming" is the creation of a dosage form by applying heat and pressure to mixtures of certain substances. *Id.* at 1250:21; 1339:22–25. First, the formulator mixes the active ingredient with a synthetic or natural polymer of high molecular weight, preferably a "thermoplastic" (heat-softening) polymer such as polyethylene oxide. '060 Patent at 11:13–14; 5:65–6:2. He may also include in the mixture "an auxiliary substance" intended to deter abuse in ways other than increasing hardness. *See id.* at 6:40–54; 11:15–19. Second, the mixture is formed by applying pressure to it, and by exposing it to heat at some point. This is where the parties disagree. Plaintiffs argue that the heat may be applied before, simultaneously to, or subsequently to the forming the tablet. Defendants argue that thermoforming does not encompass the subsequent application of heat.

The specification indicates that subsequent heat can be used to thermoform. *See id.* at 11:25–39 ("The resultant mixture is preferably formed directly by application of pressure to yield the dosage form according to the invention with preceding, simultaneous or subsequent exposure to heat."). Indeed, subsequent heat is discussed a total of five times in the patent, including in one of the patent claims *See* Claim 25; '060 Patent at 23:9. However, in an example using the subsequent application of heat, the specification inexplicably states that, "in direct tabletting with subsequent exposure to heat, the formed tablets are briefly heated at least to the softening temperature (glass transition temperature, melting temperature; sintering temperature) of component (C) and

cooled again." '060 Patent at 11:33–36 (emphasis added). The use of the words "cooled again" is baffling. If the thermoforming process encompasses the *subsequent* application of heat, how can the tablets be "cooled again"? This would imply that the tablets had been heated and cooled at some previous point rather than subsequently. Indeed, as defendants point out, Trial Tr. at 1095:14–15, none of the examples tested in the '060 Patent actually used the subsequent application of heat. *See* '060 Patent at 17–20.

The court concludes that the singular and baffling use of "cooled again" in column 11 of the '060 Patent would be insufficient to cause a person of ordinary skill in the art to exclude subsequent heat from his understanding of the term "thermoformed," given that the specification and one claim expressly allow for the subsequent application of heat.

Nor is there anything in the prosecution history of the '060 Patent to suggest the inventors had, at some point after filing the patent application, disclaimed a reading of thermoforming inclusive of the subsequent application of heat. At trial, defense counsel attempted to establish that Grünenthal had made statements to the Patent and Trademark Office removing subsequent heat from the definition of thermoforming. Trial Tr. at 1091:3–7. However, these statements were made in the prosecution of a different patent, not the '060 Patent. *See* November 27, 2006 Response to Office Action from Certified Prosecution History for U.S. Patent No. 8,114,383 (PTX-30B at 1). To the extent these statements are relevant to the '060 Patent, Grünenthal merely said "the inventive dosage forms exhibiting the desired properties may be obtained only if,

during preparation of the dosage form, the components are exposed to a sufficient pressure at a *sufficient temperature* for a sufficient period of time." *See* November 27, 2006 Response to Office Action from Certified Prosecution History for U.S. Patent No. 8,114,383 (PTX-30B at 11) (emphasis added).

As defendants suggest, "during preparation" could be read to mean "during an early" stage of the manufacturing process of the dosage form. However, when read in context, "preparation of the dosage form" does not refer to some early stage in the manufacturing process of the tablets, but to the manufacture of the tablets as a whole. *See id.* Thus, the statement to the PTO merely provided that during the manufacture of the dosage form, the components are exposed to heat. This squares completely with a definition of "thermoformed" encompassing the subsequent application of heat.

For these reasons, the court construes the terms "thermoformed dosage form" to mean "a dosage form created by applying pressure to a mixture of the active ingredient and high-molecular weight polymer and by applying the prior, simultaneous, or subsequent application of heat."

iii. The Term "Breaking" Means the Separation of the Dosage Form Into Two or More Pieces.

Claim 1 of the '060 Patent provides that the dosage form will "exhibit[] a breaking strength of at least 500 N." '060 Patent at 21:13–15. Breaking strength is the primary feature of invention. *See id.* at 2:26–30. The invention is intended to create dosage forms which are hard enough to withstand 500 newtons of force, a level of pressure so high that it would be exceedingly difficult to crush the

dosage form using household tools. *Id.* at 2:38–42.

At trial, the parties advanced different constructions of the term "breaking." No party disputed that a dosage form may deform and still be unbroken. *See, e.g.*, Trial Tr. at 2173:3–5. But plaintiffs argued that in order for a dosage form to "break," it must separate into two or more pieces. Trial Tr. at 1177:8–9. Defendants argued that "breaking" occurs earlier, when the dosage form cracks or "fractures." *See, e.g.*, *id.* at 1178:5–10. These competing constructions are relevant to infringement—if defendants' tablets "break" before 500N of force is applied, then they do not infringe the hardness claims of the '060 Patent.

Defendants' construction is at odds with the specification. The specification contemplates scenarios where the tablets deform, but explains that deformation is not tantamount to breaking. *Id.* at 17:24–26. Moreover, defendants' construction overlooks large sections of the specification describing the invention as a means for preventing comminution or *pulverization* of the dosage form. This prevention of crushing (and by extension the prevention of snorting and injecting) is the dominant theme of the specification. *See id.* at 2:26–39. When a tablet is crushed, it separates into two or more pieces, and then hundreds of pieces, which can then be snorted and injected. Thus, to be abused, the tablet *must* separate into multiple pieces. *See* '060 Patent at 1:33-35. By the same token, to be abuse-proofed, the tablet resists separation into multiple pieces when exposed to mechanical forces below 500N. *Id.* at 2:37–42. Defendants' construction of "breaking" is inconsistent with this language. A

tablet that is cracked or fractured, but not separated into multiple pieces, is useless to the abuser for snorting and injecting.

A person of ordinarily skill in the art, upon reading the specification, would understand that where it describes tablets with high breaking strength, it means tablets that will not separate into multiple pieces before 500N of force is applied. The court construes the limitation "exhibits a breaking strength of at least 500 N" to mean "only separates into two or more pieces when exposed to a force of at least 500 newtons."

Some additional terms of Claim 1 were not disputed at trial, but require construction to be fully understood. An ingredient with "abuse potential" is one susceptible to abuse, especially opiates and opioids, which are misused to obtain a euphoric state. '060 Patent at 1:25–32. Where the claim calls for "physiologically acceptable auxiliary substances," a person of ordinary skill in the art would understand this to mean a substance intended to further reduce abuse. *See* '060 Patent at 6:30–35.

In light of the above considerations, the court construes Claim 1 to read as follows:

> "A dosage form that reduces the potential for abuse which is formed by applying pressure and heat (before, during, or after pressure being applied) and comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological measurements, and optionally at least one wax (D), wherein the dosage form only separates into two or more pieces when exposed to a force of at least 500 newtons."

Plaintiffs also assert Claim 4 of the '060 Patent. Claim 4 depends from

Claim 1, and reads as follows:

> 4. A dosage form according to claim 1, Wherein the polymer (C) is at least one polymer selected from the group consisting of polyethylene oxide, polymethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers and the mixtures thereof.

'060 Patent at 21:19–24. This claim incorporates the limitations of Claim 1, but further recites that the polymer used be selected from a group of certain polymers including polyethylene oxide and others.

Claim 9 of the '060 Patent also depends from Claim 1, and reads as follows:

> 9. A dosage form according to claim 1, which additionally comprises at least one of the following components a)-f):
> (a) at least one substance which irritates the nasal passages and/or pharynx,
> (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
> (c) at least one antagonist for the active ingredient or active ingredients with abuse potential,
> (d) at least one emetic,
> (e) at least one dye as an aversive agent,
> (f) at least one bitter substance.

'060 Patent 21:37–52. Essentially, Claim 9 recites a dosage form which, in addition to meeting the limitations of Claim 1, also consists of at least one of six other barriers to abuse. *See id.* at 6:24–34. A substance that irritates the nasal passages or pharynx (part (a)) is one that brings about a strongly unpleasant physical reaction when administered via the nose or throat. *Id.* at 7:13–19. An "antagonist" (part (c)) is a substance in the dosage form which is inert when the dosage form is taken properly, but which blocks the effects of the active ingredient when the dosage form is subverted. *Cf. id.* at 9:35–67; *see also* Trial

Tr. at 985-86. An "emetic" (part (d)) is a substance that induces vomiting. A "dye as an aversive agent" (part (e)) is a dye of such brightness that it discourages abuse by injection into the vein. '060 Patent at 10:45–47. A "bitter substance" (part (f)) is one that impairs flavor to discourage oral and nasal abuse. *Id.* at 10:54–58.

iv. The Viscosity Increasing Agent Must Be Distinct From the Hardening Polymer.

As discussed, Claim 9 describes six barriers to abuse beyond the hardening feature of Claim 1. Part (b) of Claim 9 provides that the dosage form will include "at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form . . . ." '060 Patent at 21:41–45.

The definition of "viscosity-increasing agent" was never seriously disputed at trial.[3] What was disputed, however, is whether the viscosity-increasing agent of Claim 9 must be distinct from the hardening polymer of Claim 1. *See, e.g.*, Trial Tr. at 1044. As discussed, Claim 1 of the '060 Patent requires the presence of a high-molecular weight polymer. *See* '060 Patent at 21:9–11. It is this polymer which strengthens the tablet. *Id.* at 5:54–58. However, Claim 9 recites *additional* abuse-deterrent features beyond mere hardness. *See id.* at 21:37–51. One of

[3] While not disputed, the specification leaves no doubt as to the meaning of "viscosity-increasing agent." The specification explains that drug-abusers often attempt to subvert controlled-release drugs by crushing them and then mixing the resulting powder in a liquid which can be injected into the veins using a hypodermic needle. '060 Patent at 8:27–38. A viscosity increasing agent is a substance that increases the thickness of the dosage form extract by forming a gel when exposed to a liquid. *See id.* at 8:39–45. A "gel" is simply an area of thicker consistency in the mixture of the extract and the surrounding aqueous liquid, one that preferably remains visually distinguishable. *See, e.g.*, '060 Patent at 8:19–27.

these additional barriers is the use of a viscosity-increasing agent that forms a gel. The purpose of the gel is simple. It makes a tablet that has been cut and mixed with water difficult to inject intravenously. *Id.* at 8:27–38. Plaintiff Grünenthal suggests that the hardening polymer of Claim 1 can also qualify as the viscosity increasing agent of Claim 9(b). Defendants argue the opposite, that the viscosity-increasing agent must be distinct from the hardening polymer.

Defendants have the correct reading of Claim 9. Claim 9 provides that the dosage form of Claim 1 will "*additionally* comprise[]" one of the six other abuse deterrent features, one of which is a viscosity-increasing agent. '060 Patent at 21:37–38 (emphasis added). A person of ordinary skill in the art, upon reading the words "additionally comprising," would understand that the viscosity increasing agent is distinct from (in "addition" to) the hardening polymer of Claim 1. A contrary reading would render the words "additionally comprising" meaningless.

Defendants' construction is also supported by the specification examples. The specification lists six examples of dosage forms created according to the invention. Each of these dosage forms was subjected to various tests. The dosage forms in the first three examples contained no separate viscosity-increasing agent, but simply the hardening polymer polyethylene oxide. *See* '060 Patent at 17–18. These dosage forms were only tested for *hardness*, and were not tested for producing a gel. *Id.* On the other hand, the dosage forms from examples 4, 5, and 6 did contain a separate viscosity increasing agent, xanthan gum. *See* '060 Patent at 19–20. These dosage forms were tested for hardness *and* for their

gelling properties. *See* '060 Patent at 19–20. Each of them, when cut into multiple pieces and mixed with water, formed a "highly viscous gel." *E.g.*, *id.* at 20:19. The inventors' decision to test only the examples with a separate viscosity-increasing agent for gelling indicates their understanding that the hardening polymer would be distinct from the viscosity-increasing agent. This would be apparent to a person of ordinary skill in the art comparing examples 1–3 with examples 4–6.

Thus, in light of the language of the claims and the examples of the specification, the court adopts defendants' construction of "viscosity-increasing agent" as requiring a substance distinct from the hardening polymer. The entirety of part (b) of Claim 9 would read as requiring a distinct viscosity-increasing agent which, with an aqueous liquid, forms a gel that preferably remains visible when introduced into a further quantity of aqueous liquid.

Claims 22 and 23 of the '060 Patent depend from Claim 1, and read as follows:

> 22. A dosage form according to claim 1, which comprises at least one active ingredient at least partially in controlled release form.
>
> 23. A dosage form according to claim 22, wherein each of the active ingredients with abuse potential (A) is present in a controlled release matrix.

'060 Patent at 22:59–64.

Upon reading the specification, a person of ordinary skill in the art would understand that a "controlled release" dosage form is one that releases its active ingredient slowly over time. *See* '060 patent at 45–49. A "controlled release matrix," as used in the '060 Patent, may consist of hydrophilic gel-forming

materials which swell and release the active ingredient by diffusion. *Id.* at 17:20–25. The controlled release matrix may also consist of hydrophobic (water-hating) materials which release the active ingredient through pores in the matrix. *Id.* at 16:23–25.

Claim 24 depends from Claim 23, and reads as follows:

> 24. A dosage form according to claim 23, wherein component (C) and/or component (D) also serve as a controlled release matrix material.

'060 Patent at 22:65–67. This claim ultimately traces back to Claim 1, which, as discussed, has four components: (A), (B), (C), and (D). Claim 24 simply provides that the synthetic or natural polymer (C) and/or the optional wax (D) may also serve as the controlled release matrix material. *See* '060 Patent at 21:5–15; 22:65–67.

Claim 25 of the '060 Patent is a process claim. *See* '060 Patent at 23:1. Claim 27 is a product claim covering the dosage form obtained by the process according to Claim 25. *Id.* at 11–15. Together, claims 25 and 27 read as follows:

> 25. A process for the production of a dosage form according to claim 1, comprising:
>
> mixing components (A), (B), (C) and the optionally present component (D) and the optionally present components (a) to (f) to form a resultant mixture, and
>
> press-forming the resultant mixture, optionally after granulation, to yield the dosage form with preceding, simultaneous, or subsequent exposure to heat.
>
> 27. A dosage form obtainable by a process according to claim 25.

'060 Patent at 23:1–14. These claims are novel in that they refer to a process known as "press-forming." Press-forming means exactly what it sounds like: the

dosage form is created by putting the mixture in a press, with heat applied before, during, or after pressure is applied in the press. *See* '060 Patent at 11:13–19; 23:3–9. Thus, Claim 25 refers to a process of creating a dosage form using a press and the application of heat; and Claim 27 refers to the actual dosage form created as a result of that process.

Claims 28 and 29 of the '060 Patent reads as follows:

> 28. A method of treating a therapeutic condition in a patient suffering therefrom, said method comprising administering to said patient a dosage form according to claim 1.
>
> 29. The method according to claim 28, wherein the therapeutic condition is pain.

'060 Patent at 23:13–19. The term "therapeutic condition" is not defined in the patent, but would be understood as meaning a condition requiring medical treatment. Thus, Claim 28 is construed as a method claim requiring the dosage form of Claim 1 to be administered to a patient suffering from a condition requiring medical treatment. Claim 29 is identical, except that it requires the condition requiring medical treatment to be pain. *Id.* at 23:17–19.

Claims 30, 31, 32, and 33 depend from Claim 1. These claims read as follows:

> 30. A dosage form according to claim 1, wherein the polymer (C) is polyethylene oxide having a molecular weight of from 1-15 million g/mol.
>
> 31. A dosage form according to claim 1, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof.
>
> 32. A dosage form according to claim 31, which is in the form of a

> tablet.
>
> 33. A dosage form according to claim 1, wherein the content of polymer (C) is at least 60% by weight relative to the total weight of the dosage form.

'060 Patent at 23:18–24:10. Claim 30 simply repeats the dosage form of Claim 1, but provides that the polymer used will be polyethylene oxide ("PEO") with a molecular weight, or mass, of 1-15 million grams per mole. *See id.* 23:18–20. Similarly, Claim 31 requires that the active ingredient with abuse potential be oxymorphone, oxycodone, tapentadol or the salts thereof. *Id.* at 24:1–5. Claim 32 provides that the dosage form will be a tablet. Finally, Claim 33 provides that the polymer used in Claim 1 will comprise at least 60% of the total dosage form. *Id.* at 24:8–10.

Claim 34 of the '060 Patent also depends from Claim 1, and reads as follows:

> 34. A dosage form according to claim 1, which is in the form of a tablet, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof; Wherein the polymer (C) is polyethylene oxide having a molecular Weight of from l-l5 million g/mol:
>
> and wherein the content of polymer (C) is at least 30%[4] by Weight relative to the total weight of the dosage form.

'060 Patent at 24:11–19. This claim recites the dosage form according to Claim 1, but specifies that component (A) will be oxymorphone, oxycodone, or tapentadol or their salts; and that component (C) will be PEO with a mass of between 1–15 million grams per mole and will comprise 60% of the weight of the

[4] This value, 30%, was later corrected to read 60%.

dosage form.

2. Step Two: Infringement.

Having construed the claims of the '122, '216, and '060 patents, the next step is to determine whether defendants' pharmaceutical products, if manufactured and sold,[5] would infringe on those claims.

Direct infringement exists if the defendants' product or methods, as described in their ANDAs, meet each and every element of the claims. *Sunovian Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). If the defendants' products or methods fail to meet an element of the claims asserted, they may still infringe under the "doctrine of equivalents" if the differences are insubstantial. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1167 (Fed. Cir. 2012). To determine if the differences are insubstantial, the court employs the "function, way, and result" test. The missing element is insubstantial if the accused product performs substantially the same *function*, in substantially the same *way*, and achieves substantially the same *result* as each claim limitation in the asserted patent. *Id.*

Indirect infringement occurs where a defendant, rather than directly infringe the patent, induces another party to do so. *See* 35 U.S.C. § 271 (b). A person infringes by inducement when he "actively and knowingly aid[s] and abet[s] another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990). This requires a showing that the defendant knew of the patent, knowingly induced direct infringement of the

[5] Defendant Actavis is already to market with its generic product.

patent by a third party, and did so with the specific intention that the third party directly infringe the patent. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009); *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). In ANDA litigation, evidence of an intent to induce infringement of a method claim may be found if the defendant's proposed product label instructs users to perform the patented method. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010).

The requirement that the defendant induce a third party to *directly infringe* the patent raises difficulties with regard to method claims. A method claim consists of multiple steps. *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111, 2117 (2014). Of course, if the defendant itself performs all of these steps, it will be responsible for direct infringement. Likewise, if the defendant induces a third party to perform all of these steps, that third party will have committed direct infringement, and the defendant will be liable for inducing that direct infringement. *Cf. id.* A more difficult scenario is presented where a defendant induces the third party to perform some, but not all, of the steps of the method claim. In such cases, how may the defendant be liable for inducing infringement of the method claim when all of the steps of the method claim have not been performed? The answer, as the Supreme Court recently decided in *Limelight*, is that there can be no indirect infringement unless the defendant induces the third party, a single actor, to perform all of the steps provided. *Id.* at 2119 ("[A] method patent is not directly infringed . . . unless a single actor can be held responsible for the performance of all steps of the patent.").

Finally, a defendant may also commit contributory infringement. Contributory infringement occurs when a defendant makes a component he knows will be used by others to make an infringing product or to conduct an infringing method. See 35 U.S.C. § 271(c). To prove contributory infringement of a method claim, the plaintiff must show that: "there is direct infringement; the accused infringer [the defendant] had knowledge of the patent at issue; the component has no substantial non-infringing uses; and the component is a material part of the invention." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010) (internal numbering omitted).

a. Infringement With Regard to the '122 and '216 Patents.

As demonstrated in the claim construction section of this decision, Endo asserted an unusually large number of claims in these actions. Endo asserted four claims[6] with regard to the '122 Patent; and sixteen claims[7] with regard to the '216 Patent. This large number of claims is not as unwieldy as it may seem, however, because most of the claims repeat common elements. More significantly, defendants do not dispute infringement of most of the asserted claims. In stipulations dated March 27, 2015 and April 9, 2015, defendants agreed that their tablets "satisfy each limitation of each '122 and '216 patent claim asserted against them" except with regard to two issues: (i) whether their tablets satisfy the "food effect limitations" of the asserted claims; and (ii) whether

[6] Claims 2, 3, 19, and 20.
[7] Claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, 82 (not all claims asserted against all defendants).

defendants infringe the asserted method claims. *See* Stipulation and Order at 1, No. 12-CV-8060 (Mar. 27, 2015) (Dkt. #152); *see also* Second Stipulation and Order at 1, No. 12-CV-8060 (Apr. 9, 2015) (Dkt. # 154).

i. Whether Defendants' Tablets Satisfy the Food Effect Limitations of the Asserted Claims of the '122 and '216 Patents.

Defendants argue that their tablets do not satisfy the food effect limitations embodied in Claim 20 of the '122 Patent and claims 40, 42, 50, 54, 78, 80, and 82 of the '216 Patent. The "food effect" refers to a patient's physiological response to a drug after having eaten. For example, a patient who takes a drug with a pronounced food effect might experience much higher concentrations of the active ingredient if he has recently eaten. *See* Trial. Tr. at 298. Part of the invention claimed by Endo is a dosage form that addresses this "food effect," keeping the concentration of oxymorphone in the bloodstream at an acceptably constant rate regardless of whether a patient has eaten or has fasted. *See id.* at 299–300. Defendants argue that their tablets would not or do not infringe on the several food effect limitations of the '122 and '216 Patents.

Defendants infringe the food effect limitations of the '122 and '216 Patent if their tablets, upon being administered to a patient, produce the following effects: (1) the maximum observed concentration (C_{max}) of oxymorphone in the bloodstream is at least 50% percent higher after having eaten a meal than it would be on an empty stomach; and (2) the subject exhibits total blood concentration levels ($AUC_{(0\text{-}inf)}$) levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the dosage form on an

empty stomach.

At trial, Endo's expert on infringement, Dr. Reza Fassihi, testified that the defendants' submissions to the FDA prove that their drug products infringe or will infringe on the food effect limitations of the '122 and '216 Patents. Trial Tr. at 637:6. Dr. Fassihi explained that in order to obtain approval to sell a branded or generic drug, the FDA requires an applicant to demonstrate the drug's food effect, if any. *Id.* at 641. In the case of a new branded drug, the applicant performs food-effect studies, which measure the effect of the drug in groups of human subjects who have been fed or who have fasted. *See id.* at 638:10–19. The resulting data will demonstrate to the FDA whether a food effect exists. On the other hand, a generic drug applicant seeking FDA approval is not required to perform new food effect studies. *Id.* at 641. Rather, the generic manufacturer may submit to the FDA information showing that their proposed drug will have the same effects as the branded drug. *Id.* This is the course each of the defendants chose. Based on the information defendants provided to the FDA, Dr. Fassihi concluded that their generic products infringe or will infringe on the food effect limitations of the asserted patent claims.

In reaching his conclusion, Dr. Fassihi relied heavily on defendants' "package inserts." A package insert is included with the drug, and provides information to patients and doctors on how to correctly take and prescribe the tablets. *Id.* at 643:15–20. Defendants' package inserts expressly state that their products satisfy the AUC and C_{max} limitations of the '122 and '216 patents. *See, e.g.*, Actavis CRF Package Insert (PTX-2436 at 21) ("C_{max} was increased by

approximately 50% in fed subjects compared to fasted subjects . . . . The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects.); *see also* Roxane Package Insert (PTX-3070 at 4). Each of defendants' package inserts contains this information. Trial Tr. at 647:16-18 ("Every defendant has the same feed-effect information and package insert for the pills that they have made.").

Dr. Fassihi also relied on defendants' statements to the FDA that their proposed generic drugs are bioequivalent to Endo's branded drugs. *See* Trial Tr. at 717. Each defendant conducted bioequivalence studies to show that their drug does not differ significantly from Endo's branded drugs. *See, e.g.*, Actavis Bioequivalence Study (PTX-2385). This is important because Endo, in drafting the '122 and '216 Patents, recited limitations reflecting their extensive clinical and laboratory testing of dosage forms that would become OPANA®ER. Indeed, the asserted claims of the patents, including the food effect claims, are drawn around studies Endo performed during the testing and development of the branded product. *See* Trial Tr. at 482. For example, one of Endo's studies, highlighted in the specifications of the patents, showed an oxymorphone peak concentration level (C_{max}) 58% higher under fed conditions as compared to fasted conditions. *See, e.g.*, '216 Patent at 17:43–46. The relevant patent claim, then, called for a C_{max} greater than 50% under fed conditions as compared to fasted conditions. *See, e.g.*, '216 Patent at 30:3–5.

Dr. Fassihi reasoned that defendants, by demonstrating to the FDA that their products are bioequivalent to OPANA®ER and OPANA®ER CRF, also

demonstrated that their products exhibit the same food effects as those branded drugs. Trial Tr. at 717. The court finds him to be persuasive in explaining this inference. The bioequivalence of the products described in defendants' ANDAs indicates that those products will exhibit the same pharmacokinetic properties as Endo's branded drug, the effects of which are embodied in relevant claims of '122 and '216 Patents.[8] Trial Tr. at 716. The court need not rely solely on this inference, however. As discussed, Dr. Fassihi referred to defendants' package inserts in reaching his conclusions on infringement. He also considered defendants' product labels, dissolution test data, requests for bio-waivers, approval letters, and other evidence. *See* Trial Tr. at 654–55.

On cross-examination, defendants argued that Dr. Fassihi should have performed his own food effect studies of defendants' products to determine infringement, rather than rely on their submissions to the FDA. Trial Tr. at 722–724. Having heard Dr. Fassihi's testimony, the court concludes that such independent testing was unnecessary. Dr. Fassihi's review of Defendant's ANDA submissions, including defendants' package labels and other documentation, revealed sufficient evidence of infringement to meet plaintiffs' burden. To require plaintiffs to perform independent clinical testing of each of defendants products would put them to a burden beyond a preponderance of the evidence.

The court concludes, upon hearing the credible testimony of Dr. Fassihi, and upon reviewing the documents he relied on, that it is more likely than not

[8] Another of Endo's experts, Dr. Stephen Ogenstad, used statistical methods to show that Endo's product, OPANA®ER in both crushable and non-crushable formulations, actually satisfies the limitations of the asserted claims. *See* Trial Tr. at 2089–92.

that defendants' generic drug products, as described in their ANDAs, would satisfy the food effect limitations of the asserted claims of the '122 and '216 patents.

ii. Whether Defendants Infringe the Asserted Method Claims of the '122 and '216 Patents.

Defendants argue that they do not infringe the asserted method claims of the '122 and '216 Patents. With regard to direct infringement, defendants argue that they do not directly infringe the claims because they simply make and sell tablets and do not actually administer them to patients. *See* Trial Tr. at 613:18 ("We just manufacture pills . . . we don't ever administer the pill to the patient."). With regard to indirect infringement, defendants argue that: (1) their product labels do not instruct subjects to take the tablets under fed *and* fasted conditions, thus defendants do not induce infringement of the method claims that have food effect components; and (2) no single person performs all of the steps of the asserted method claims, and since there is no direct infringement by any single person, there can be no indirect infringement Trial. Tr. at 530:12–13 (referring to the Supreme Court's decision in *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111 (2014)).

Defendants are correct in that they, as drug manufacturers, do not directly infringe the asserted method claims of '122 and '216 Patents. Defendants do not feed tablets to patients or subjects, and thus do not "administer" them as required in Claim 20 of the '122 Patent, as required in part (b) of Claim 38 of the '216 Patent (and the asserted claims, claims 40 and 42, that depend from it), and as required by Claim 82 of the '216 Patent. Thus, defendants cannot be

liable for direct infringement.

With regard to indirect infringement, defendants are incorrect to argue that they must instruct patients to take their tablets under fed and fasted conditions.

Defendants have submitted to the FDA proposed product labels for their generic oxymorphone products. *See* Trial Tr. at 517:1–4. These product labels instruct patients to take the generic tablets on an empty stomach. *See, e.g.*, DTX 3542 at 2244. At trial, defendants' expert on non-infringement, Dr. Timothy Deer, testified that in prescribing generic oxymorphone tablets to patients, he and his colleagues are careful to instruct them according to the product labels. Trial Tr. at 517:1–14. Thus, defendants argue that since their labels do not instruct patients to take the tablets under fed conditions, they do not induce infringement of the "food effect" portions of the asserted method claims.

This argument relies on an unsupported reading of the asserted method claims. The most complicated of the method claims, claims 40 and 42 of the '216 Patent (both of which depend from Claim 38), consist of two parts and require that the tablets be provided to the subject, and then administered to that subject.[9] *See* '216 Patent at 29:49–30:40 ("A method for treating pain in a human subject . . . comprising the steps of: (a) providing a solid oral dosage form . . . and (b) administering a single does . . . to the subject . . . ."). The claims then go further, stating that the composition that was administered, *upon being tested*,

[9] The other asserted method claims, Claim 20 of the '122 Patent and Claim 82 of the '216 Patent, do not require that the tablet first be "provided" to the subject. *See, e.g.*, '216 Patent at 34:56–60. They merely require administration of the tablet. *Id.*

will exhibit certain *in vitro* and *in vivo* characteristics. *See, e.g.*, *id.* at 29:51–67. ("Wherein upon placement of the composition in an *in vitro* dissolution test comprising . . . ."). Similarly, Claim 20 of the '122 provides that upon oral administration of the tablet, the subject will exhibit higher blood concentrations of oxymorphone if he has eaten than if he had taken the tablet on an empty stomach. '122 Patent at 1–5.

This language indicates that it is not necessary to the completion of the methods that the tablet be taken under fed *and* fasted conditions. Rather, the methods are completed once the tablets are administered. Once the tablets are administered, the subject will exhibit different pharmacokinetic effects depending on whether he has eaten or fasted. *See, e.g.*, '216 Patent at 15–28; *see also* '122 Patent at 1–5. It is the taking of the qualifying tablet (one that will produce the claimed pharmacokinetic effects) that constitutes the method claimed. Once a patient administers the qualifying tablet, he directly infringes the method claims.

Thus, it is not necessary for defendants to instruct subjects to take the tablets under fed *and* fasted conditions. By instructing subjects to take the tablets at all, defendants assure that patients will complete the methods asserted in the '122 and '216 patents. Once patients have followed defendants' instructions and infringed the method claims, their blood will exhibit certain pharmacokinetic characteristics. *See, e.g.*, '216 Patent at 30:18–19 ("the dosage form provides detectable levels of 6-OH oxymorphone and oxymorphone."). Those characteristics will be different if the patient has recently eaten. But the method

performed—the administration of the tablet—will be the same.

This puts to rest defendants' argument regarding instruction, but the court must still resolve the question of whether a single actor performs all of the steps of the asserted method claims. As discussed, the Supreme Court has recognized that indirect infringement of a method claims requires proof of *direct infringement* by some third party. *Limelight*, 134 S. Ct. at 2117. But there can be no direct infringement by a third party unless that party has itself performed all of the required steps of the asserted method. *Id.* Thus, indirect infringement requires proof, by a preponderance of the evidence, that defendants induce a single party to perform all of the steps of the asserted method claims.

There is clear indirect infringement with regard to claims 20 of the '122 Patent and 82 of the '216 Patent. The methods recited in these claims is merely the administration of the dosage form to the subject. Defendants, through their product labels, instruct subjects to take qualifying generic oxymorphone tablets. *See, e.g.*, DTX-3542, DTX-3523; DTX-3563. In doing so, they demonstrate a specific intention to induce infringement. *See DSU Med. Cor. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). The subjects then perform all of the steps of the methods recited in those claims, because they "administer," or take orally, defendants' tablets. *See* '122 Patent at 26:54–56, 28:1–5; '216 Patent at 34:56–60. Once the method is completed, the subjects' blood will exhibit certain concentrations of oxymorphone depending on whether they have eaten or have fasted. '122 Patent at 28:1–5. Thus, there is clear indirect infringement of claims 20 of the '122 Patent and 82 of the '216 Patent.

It is a closer question as to whether a single party performs all of the steps of claims 40 and 42 of the '216 Patent. As discussed, these claims require the tablet to be provided *and* administered to subjects. Dr. Deer, testified that multiple parties perform these two steps. As a prescribing physician, he performs the first step, providing the tablets, by making them available to patients. Trial. Tr. at 522:15–25. This step is also performed when a pharmacy fills the prescription. *Id.* at 523:1–19. The second step, "administration," occurs when the patient takes the pill orally. Thus, according to Dr. Deer, up to three parties are involved in performing the methods recited in claims 40 and 42 of the '216 Patent. Trial Tr. at 524:6–9 ("[A]t least three people are involved in this process, a physician, a pharmacy, and a patient."). This would indicate that there can be no indirect infringement because no single party can be liable for direct infringement.

On the other hand, Endo's expert on infringement, Dr. Fassihi explained that physicians and nurses in a hospital setting often perform both the "provide" and "administer" steps by directly giving patients tablets to swallow. *See* Trial Tr. at 656–57. This would imply that there is indirect infringement, since defendants induce a single party to perform the entire method claimed.

The court finds Dr. Deer to be more persuasive on this question. Defendants, through their product labels, instruct physicians to prescribe tablets to patients. By writing prescriptions for the tablets, physicians perform the first step of the methods recited in claims 38, 40, and 42 of the '216 Patent by making tablets available to patients. However, in the majority of cases, it is

the patient who performs the second step and administers the tablet at home to treat chronic pain. While there may be isolated settings where physicians physically insert tablets into patients' mouths, *see* Trial Tr. at 657:1–7, plaintiffs did not provide the court with sufficient evidence to find that this happens with any degree of regularity. Thus, plaintiffs have not shown that it is probable that a single actor performs all of the steps of the methods recited in claims 40 and 42 of the '216 Patent, and there is no direct infringement of those claims. Since there is no direct infringement, defendants cannot be liable for indirect infringement of claims 40 and 42.

For similar reasons, contributory infringement is also unavailing with regard to claims 40 and 42 of the '216 Patent. While Endo has satisfied most of the elements of its contributory infringement claim (by showing no-substantial non-infringing use; knowledge, and materiality); *see* Trial Tr. at 668, it did not show that there is direct infringement of the methods recited in claims 40 and 42. Again, Endo has not submitted sufficient evidence showing that any third party directly infringes the method of claims 40 and 42 of the '216 Patent by both "providing" and "administering" the dosage form to subjects. Thus, without direct infringement, there can be no contributory infringement. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 483 (1964) ("There can be no contributory infringement in the absence of a direct infringement.").

The court makes the following conclusions with regard to infringement of the '122 and '216 patents. The court concludes that plaintiffs have satisfied their burden in showing that defendants' generic drug products, as described in their

ANDAs, infringe the food effect limitations of the asserted claims. The court concludes that defendants indirectly infringe method claims 20 of the '122 Patent and 82 of the '216 Patent. However, the court concludes that plaintiffs have failed to satisfy their burden and show indirect infringement of claims 40 and 42 of the '216 Patent. Thus, defendants infringe all of the asserted claims except those two.[10]

b. Infringement With Regard to the '060 Patent.

Grünenthal presented evidence of infringement of the '060 Patent against Actavis, Impax, ThoRx and Teva.

As discussed above, the '060 Patent is the product of Grünenthal's efforts to produce a tablet so hard that it is resistant to abuse through crushing, and which also accommodates other barriers to abuse. As with the '122 and '216 patents, plaintiffs have asserted an unusually large number of claims of the '060 patent. However, determining infringement of these claims is straightforward, involving five issues. These issues are whether defendants' tablets: (i) are abuse-

[10] To be specific, through their stipulations and the court's findings, each of the defendants infringes claims 2, 3, 19, and 20 of the '122 Patent. Through their stipulations and the court's findings, the following conclusions apply with regard to the '216 Patent. Defendant Actavis, in case No. 13-cv-436, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Amneal, in case No. 12-cv-8115, is liable for infringement of claims 1, 22, 50, 54, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant ThoRx, in case No. 12-cv-8317, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Impax, in case No. 13-cv-435, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, and 71 of the '216 Patent. Defendant Teva, in case No. 12-cv-8060, is liable for infringement of claims 1, 22, 50, 54, 62, 64, 71, 73, 74, 78, 79, 80 and 82 of the '216 Patent. Defendant Sun Pharmaceuticals, in case No. 13-cv-8597, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent. Defendant Actavis, in case No. 12-cv-8985, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Roxane, in case No. 13-cv-3288, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent. Defendant Sun Pharma, in case No. 13-cv-4343, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent.

proofed; (ii) are "thermoformed"; (iii) have a breaking strength of at least 500 newtons; (iv) have a "viscosity-increasing agent" which "forms a gel" with the extract obtained from the dosage form; and (v) whether plaintiffs have shown infringement of the remainder of the asserted claims.

i. Whether Defendants' Tablets Are Abuse-Proofed.

Claim 1 of the '060 Patent describes a dosage form that is "abuse-proofed." *See* '060 Patent at 21:6. The portions of the trial dealing with this limitation focused primarily on issues of claim construction, specifically, whether "abuse-proofed" requires a demonstrated elimination of abuse, or whether it simply requires a reduction in the potential for abuse. *See, e.g.*, Trial Tr. at 1137:7–11. As the court determined in the claim construction section of this decision, a person of ordinary skill in the art would understand the term "abuse-proofed" as merely requiring a reduction in the potential for abuse. *See supra* Part A(1)(c)(i).

At trial, defendant Actavis was the only party to dispute whether its tablets are "abuse-proofed." Trial Tr. at 1137:4. During his direct testimony, defendants' expert on non-infringement, Dr. Muzzio, stated that the issue regarding "abuse-proofed" was not that it required a complete eradication of all abuse, but that it required some factual showing that a tablet achieves a significant elimination of abuse. Trial Tr. at 2151–52. Dr. Muzzio testified that plaintiffs have failed to show that defendants' tablets actually cause a significant elimination of abuse, and thus have failed to meet their burden in showing infringement. *Id.*

Plaintiffs have met and exceeded their burden of showing that defendants' tablets reduce the potential for abuse. As will be discussed below, plaintiffs'

expert, Dr. Stanley Davis, tested defendants' generic products and showed that they exhibit an exceptionally high breaking strength. *See infra* Part A(2)(b)(iii). Dr. Davis explained that the hardness of defendants' tablets reduces their potential for abuse by making it more difficult to grind the dosage form into a powder suitable for snorting and injecting. Trial Tr. at 1150:18–22. This is not mere speculation. Indeed, in Actavis's submissions to the FDA, it repeatedly refers to its generic product as "crush-resistant." *See, e.g.*, PTX 2369[11]. at 3970. When Actavis tested its tablets using a mortar and pestle, they flattened into a "pancake" shape but did not crumble into a powder. *Id.* ("Both crushed tablets resembled a pancake.").

In the court's view, it is absurd to argue that a crush-resistant tablet fails to reduce the potential for abuse to some extent. Of course, a drug abuser who fails to crush a hard tablet may take other efforts to subvert the tamper-resistant properties of the drug. *See, e.g.*, Letter from the FDA to Robert Bart (May 10, 2014) at 5 (DTX 5032) ("[E]xtended-release features can be compromised . . . when subjected to other forms of manipulation . . . ."). But this does nothing to diminish the fact that the tablet reduces the potential for abuse of the dosage form by crushing.

A crush-resistant tablet reduces the potential for abuse through crushing, and is thus "abuse-proofed." Having heard the testimony of Dr. Davis, *see infra*

[11] Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. *See* Trial Tr. at 1209, and the court rules that it is relevant and not otherwise inadmissible. *See* Fed. R. Evid. 402.

Part A(2)(b)(iii), and Dr. Muzzio, and upon reviewing the exhibits they relied on, the court is satisfied that defendants' generic products are "abuse-proofed" as required by Claim 1 of the '060 Patent.

ii. Whether Defendants' Tablets are Thermoformed.

Each of the asserted claims of the '060 Patent require a "thermoformed dosage form." *See, e.g.*, '060 Patent at 21:6. As determined in the claim construction section of this decision, a "thermoformed dosage form" is a "dosage form created by applying pressure to a mixture of the active ingredient and high-molecular weight polymer and applying the prior, simultaneous, or subsequent application of heat." *See supra* Part A(1)(c)(ii).

Defendants' ANDAs describe the process used in manufacturing their generic oxymorphone tablets. Defendant Actavis uses a fixed-speed blender to mix oxymorphone hydrochloride with the hardening polymer. See Trial Tr. at 1170, *see also* PTX-2372[12] at 24645. It then compresses the mixture in a rotary tablet press with a force feeder. PTX-2372 at 24645. Actavis cures the mixture by applying 65–72°C of heat. *Id.* at 24649. [redacted] PTX-2766 at 0389; PTX-3413 at 0415. Teva's manufacturing process involves first blending the ingredients, and then compressing the mixture in a tablet press. *See* PTX-3257 at 0399. Teva

[12] Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. *See* Trial Tr. at 1169, and the court rules that it is relevant and not otherwise inadmissible. *See* Fed. R. Evid. 402.

then heats the compressed mixture for 15–90 minutes, and coats them. *See* PTX-3257 at 0399.

The court concludes that because thermoforming encompasses manufacturing processes involving the subsequent application of heat, each of the defendants' tablets are "thermoformed" as required by Claim 1 of the '060 Patent.

iii. Whether Defendants' Tablets Have a Breaking Strength of at Least 500N.

Defendants argue that their generic oxymorphone tablets do not have a breaking strength of at least 500N, and therefore do not infringe any of the asserted claims of the '060 Patent. *See, e.g.*, Trial. Tr. at 151–53.

As discussed in the claim construction portion of this decision, a tablet is "broken" when it separates into two or more pieces. *See supra* Part A(1)(c)(iii). Thus, to satisfy its burden on infringement, Grünenthal must prove by a preponderance of the evidence that defendants' tablets are unbroken, or not separated into two or more pieces, when subjected to a pressure of at least 500N.

Dr. Davis tested each of defendants' tablets to determine whether they broke when subjected to pressures of at least 500N. *See* Trial Tr. at 1185. He used a sophisticated protocol in doing so. Using a calibrated Instron testing device, Dr. Davis took ten of each dosage strength of defendants' tablets and applied 503 newtons of force to them. *See* Trial Tr. at 1279:9–11. After being squeezed by the Instron testing device, Dr. Davis's assistant removed the tablets and placed them onto a "data form," or a sheet of paper with labels identifying

the tablets. *Trial Tr.* at 1191–92. Dr. Davis then took photographs of all of the tablets. Upon studying these photographs, Dr. Davis observed that while some of the tablets had deformed, none of them had broken into two or more pieces. Trial Tr. at 1192:22–24.

Dr. Davis also created "compression curves" of defendants' tablets, showing the extent to which the tablets compressed, or flattened, when subjected to pressures between zero and 504 newtons. *See, e.g.*, PTX 2567. Based on his observations, Dr. Davis concluded that defendants' tablets are sufficiently hard as to infringe the breaking strength limitation of Claim 1 of the '060 Patent. Trial Tr. at 1194.

Dr. Muzzio reviewed Dr. Davis's photographs, and with regard to defendant Actavis, concluded that some of the tablets had, in fact, separated into two or more pieces upon being tested at 503N. Trial Tr. at 2122:2–3 ("If anything, these pictures show broken tablets. You see dust and pieces falling off."). Dr. Muzzio also reviewed Dr. Davis's compression curves. Trial Tr. at 2122–23. He interpreted the compression curves as showing that that defendants' tablets "break" before 500N because at some point they continue to flatten without requiring the application of additional force. *See* Trial Tr. at 2123:9–19.

Defendants also argued that rather than simply rely on Dr. Davis's photographs of the tablets, those tablets should have been brought to court so the court could make the factual determination of whether they are broken. *See* Letter from Charles Weiss to the Court at 2 (Feb. 25, 2015); No. 13-CV-436 (ECF #75). The court initially agreed, stating "It would be helpful to the court, as the

finder of fact, for the tablets to be available at trial if needed in either party's presentation." Order of Mar. 19, 2015, No. 13-CV-436 (ECF #118). However, as trial approached, Grünenthal found it impossible to secure release of the tablets from the facility in which they were stored, given that they are a controlled substance. *See* Letter from Jennifer Roscetti to the Court at 3 (Mar. 9, 2015), No. 13-CV-436 (ECF #94) ("Actavis feigns ignorance as to the legal burdens of handling and transporting a Schedule II controlled substance pursuant to the Controlled Substances Act . . . ."). Given Grünenthal's concerns, the court settled on an intermediate solution, allowing Actavis to travel to Grünenthal's expert's testing facility in Pennsylvania to make its own inspection of the tablets. *See* Trial Tr. at 229–230. The court then instructed Grünenthal that it need not produce the actual tablets at trial. Trial Tr. at 230:3–5 ("If you can [produce the tablets], fine. If you can't [produce them], we'll do without.").

In the end, having heard the testimony of Dr. Davis and Dr. Muzzio, and having examined photographs of the tablets taken both when they were tested and on the eve of trial,[13] the court finds that defendants' tablets, in every dosage strength, remain unbroken when subjected to 503 newtons of force. *See, e.g.*, (PTX 2554); (PTX 2593); (PTX-2700); and (PTX-2661). It is true that two of the

[13] Defendants note that upon visiting the Emerson Testing Facility during trial, the tablet pills were in far worse condition than when originally tested. *See* Trial Tr. at 1295–98. Moreover, the tablets had been covered in scotch tape. Trial Tr. at 1298:2–6. Defendants argue that Grünenthal, by covering the tablets with scotch tape after testing them, obscured the fact that they separated into multiple pieces after being tested. *Id.* at 1299:1–4. The court draws no such conclusions from Grünenthal's post-testing conduct. It is not surprising that the tablets, having been stored for a year, would be in a different condition than when initially tested. Moreover, Grünenthal's decision to cover the tablets with tape prior to storing them was reasonable given that testing was complete.

Actavis 30mg tablets tested showed significant deformation, and exhibited large fractures, in Dr. Davis's photographs. *See* PTX2569 at 0063. Similarly, a photograph of one of the tested Teva tablets, the 10mg tablet, shows a flake separated from the dosage form. *See* PTX 2667 at 0036. But these are the results of just three tests. Each dosage strength was in fact tested ten times. Thus, even though a photograph of one Teva's 10mg shows a flake, the other nine photographs of Teva's 10mg tablet show completely unbroken tablets. *See* PTX 2667 at 0036. The same is true of eight out of ten Actavis 30mg tablets, which show no hint of separating into two or more pieces. *See* PTX2569 at 0063. Given that each tablet was tested ten times, and that the overwhelming majority of tests indicated no hint of separating into two or more pieces, the court finds it probable that the Actavis 30mg tablets and Teva 10mg tablets have a breaking strength of more than 500N. The same is true regarding the other dosage strengths. Dr. Davis's photographs prove, by a preponderance of the evidence, that these tablets remain unbroken at pressures above 500N. Thus, the court concludes that defendants infringe the breaking strength limitation of the '060 Patent.

iv. Whether Defendants' Products Have a Separate Viscosity-Increasing Agent Which Forms a Gel With the Extract From the Dosage Form.

Claim 9 of the '060 Patent takes the dosage form described in Claim 1 and incorporates additional barriers to abuse beyond hardness, such as the use of an emetic, a nose/throat irritant, a dye, a "viscosity increasing agent," *et cetera*.

See '060 Patent at 21:37–52. Of these additional barriers to abuse, the only one that could possibly be found in defendants' products is the "viscosity-increasing agent," which when exposed to an aqueous liquid "forms a gel with the extract obtained." Trial Tr. at 149; '216 Patent at 21:41–46 (Claim 9 part (b)). The purpose of this additional barrier is to complicate abuse by injection. A drug abuser, upon attempting to dissolve a subverted tablet in a liquid, will discover that it forms a gel that is difficult to inject by needle. *See* Trial Tr. at 987.

As discussed in the claim construction section of this decision, the '060 Patent would be read by a person of ordinary skill in the art as requiring the viscosity-increasing agent to be distinct from the hardening polymer. *See supra* Part A(1)(c)(iv). Thus, Grünenthal must show that defendants' tablets, beyond having a hardening polymer, use some other substance, such as xanthan gum, to provide increased viscosity. It fails in this burden with regard to each of the four defendants. Neither Actavis, Impax, ThoRx, nor Teva[14] have been shown to include a distinct viscosity-increasing agent, such as xanthan gum, in their generic products.

While defendants' products do not contain a separate viscosity-increasing agent, the court nonetheless concludes that defendants infringe part (b) of Claim 9 pursuant to the doctrine of equivalents. Each of defendants' tablets, as discussed, contain polyethylene oxide ("PEO"), At trial, Dr. Davis explained that

[14] Defendant Teva did not dispute whether its product has a separate viscosity increasing agent. Trial Tr. at 1202:18–20. Nonetheless, it is Grünenthal's burden, as plaintiff, to show that Teva's drug infringes the asserted claims. Grünenthal has not shown that Teva's product contains a viscosity-increasing agent distinct from polyethylene oxide. *See* PX-5002.215; *see also* PTX 2657 at 5.

the PEO in defendants' tablets performs substantially the same function, in the same way, and achieves the same result as the xanthan gum in Endo's tablets. Trial Tr. at 1203.

The PEO in defendants' tablets makes it more difficult for abusers to prepare defendants' tablets for intravenous injection. This is because the PEO, aside from providing hardness, also functions to increase viscosity of the extract when exposed to water. *See* Trial Tr. at 1203–04. It does this in the same way as the xanthan gum in plaintiffs' products, by mixing with the aqueous liquid. Trial Tr. at 1204:2–6. It also achieves the same result as the xanthan gum in Endo's tablets. When defendants' tablets are milled and placed in a spoon containing water, the PEO forms a "slimy stick paste" that cannot be poured from the spoon. *See* Trial Tr. at 1204:19-21; *see also* Actavis Introduction to Overall Quality Summary (PTX-2367[15] at 23622). Thus, the PEO in defendants' tablets, by performing the same function in the same way as a separate viscosity-increasing agent, and by achieving the same result, infringes part (b) of Claim 9 of the '060 Patent.

At trial, defendants argued that their products do not "form a gel" as required by the remainder of part (b) of Claim 9 of the '060 Patent. However, defendants' own submissions to the FDA, and Dr. Davis's testing of their tablets, show otherwise. As discussed, Actavis reported to the FDA that its milled tablets

[15] Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. *See* Trial Tr. at 1169, and the court rules that it is relevant and not otherwise inadmissible. *See* Fed. R. Evid. 402

formed a "slimy sticky paste" when combined with water in a spoon. (PTX-2367 at 23622). In the court's view, there is no significant difference between a "slimy sticky paste" and a "gel." The court need not rely on semantics, however, to resolve whether defendants' tablets "form a gel." Dr. Davis, in testing defendants' tablets, assessed each of them for whether they formed a gel when milled and placed in a vial of water. *See* Trial Tr. at 1359–60. The results of these tests, captured in photographs, speak for themselves. Each of defendants' tablets form a thick and unmistakable gel when milled and placed in water. *See, e.g.*, PTX-2577 (showing the results of "gel testing" Actavis's 7.5mg tablet).

Grünenthal has satisfied its burden and shown by a preponderance of the evidence that defendants' tablets infringe Claim 9 of the '060 Patent. Although their tablets do not contain a distinct viscosity-increasing agent as required by the claim, the PEO in their tablets satisfies the limitation under the doctrine of equivalents. Moreover, each of defendants' tablets forms a gel as required by the claim.

v. Whether Defendants Infringe The Remaining Limitations of the Asserted Claims.

Having resolved the issues disputed at trial, the remainder of the infringement inquiry is straightforward. Grünenthal has proved by a preponderance of the evidence that defendants infringe the asserted composition and method claims of the '060 Patent.

With regard to Claim 1, defendants' tablets are, as discussed, "abuse-proofed thermoformed dosage forms." Because defendants' products contain the opioid oxymorphone, they indisputably have an "active ingredient with abuse

potential" as required by the claim. *See* '060 Patent at 21:6-7. Moreover, the hardening polymer used in defendants' tablets, polyethylene oxide, satisfies part (C) of the claim. *Id.* at 21. Finally, as discussed above, defendants' tablets satisfy the final limitation of the claim because they exhibit a breaking strength of at least 500N. Thus, defendants products infringe Claim 1 of the '060 Patent.

Because defendants' tablets use polyethylene oxide as the hardening polymer, they infringe Claim 4 of the '060 Patent. *See* '060 Patent at 19:20–23 ("wherein the polymer is at least one polymer selected from the group consisting of polyethylene oxide . . . ."). Since the tablets are in a controlled release form, and because the PEO in them serves as the controlled release matrix material, defendants infringe on Claim 24 of the '060 Patent. Moreover, defendants' tablets satisfy the limitations of claims 25 and 27 because they are made by mixing the components of Claim 1, press-forming that mixture, and then subsequently exposing it to heat. *See, e.g.*, Trial Tr. at 2548; *see also* '060 Patent at 23:1–12; DTX-2192 at 1236. Defendants induce infringement of the method recited in Claim 29 by instructing patients to administer the tablets to treat pain. *See, e.g.*, PTX-2352. Defendants' tablets infringe Claim 30 because their hardening polymer, Polyox (the commercial version of polyethylene oxide) has a molecular weight above one million grams per mole. Trial Tr. at 1202:4–5. Defendants' products satisfy claims 31 and 32 because they use oxymorphone as the active ingredient, and the dosage form is a tablet. They satisfy Claim 33 because the polyethylene oxide in their tablet comprises more than 60% of the dosage form by weight. *See, e.g.*, PTX-2589 at 10; PTX-2657 at 12. Likewise, each of the

defendants except for Teva, against whom it is not asserted, infringe Claim 34 of the '060 Patent because the content of their hardening polymer, polyethylene oxide, is at least 60% by weight relative to the dosage form.

The court concludes that plaintiffs have satisfied their burden and shown by a preponderance of the evidence that Actavis, Impax, ThoRx, and Teva infringe claims 1, 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34[16] of the '060 Patent.

B. Whether the Patents-in-Suit are Invalid.

An invention is only patentable if it is novel. *See* 35 U.S.C. § 101. An invention is novel if there is no substantially identical matter disclosed by a piece of prior art. *See* 35 U.S.C. § 102(a). It goes without saying that an invention is not novel, and is therefore not patentable, if it simply recites a law of nature, natural phenomenon, or abstract idea. *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). If an invention touches on natural phenomena, to be patentable it must provide additional elements such that the practice of the invention amounts to more than the practice of the natural phenomenon. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). In addition to being novel, an invention must also be useful. *See* 35 U.S.C. § 101. An invention is "useful" if it confers substantial utility to society, meaning it provides some practical benefit to the public. *See Brenner v. Manson*, 383 U.S. 519, 534–35 (1966); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005).

Once awarded, a patent is presumed to be valid. 35 U.S.C. § 282(a). In an

[16] Plaintiffs did not assert Claim 34 of the '060 Patent against Teva, so the court makes not findings or conclusion as to whether Teva infringes that claim.

action for patent infringement the defendant, regardless of whether it asserts non-infringement of the claims, may argue that the patent itself is invalid. 35 U.S.C. § 282(b). The defendant carries a heavy burden in this regard. It must prove the patent's invalidity by clear and convincing evidence, *Microsoft Cor. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242–43 (2011), meaning evidence that instills in the court an "abiding conviction" that the patent's invalidity is highly probable. *ActiveVideo Networks, Inc. v. Verizon Communications, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012).

Generally speaking, a defendant may prove the invalidity of a patent by showing that it is anticipated by a single prior art reference; or would have been obvious to a person of ordinary skill in the art at the time of the invention. *See* 35 U.S.C. §§ 102, 103. A patent will also be invalid if, more than a year before the patent application was filed, the invention was both ready for patenting and the subject of a commercial offer for sale, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998); or if the patent fails to provide a sufficient written description of the invention, fails to enable use of the invention, or is indefinite. *See* 35 U.S.C. § 112(a).

Anticipation requires that a single prior art reference disclose every element of the claimed invention. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). If the prior art reference fails to disclose a feature of the invention, it will only anticipate the invention if the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Id.*

To establish obviousness, a defendant "must demonstrate by clear and

convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706–07 (Fed. Cir. 2012). In determining whether a patent claim is obvious, the court will consider "the scope and content of the prior art; the level of ordinary skill in the art; the differences between the claimed invention and the prior art; and evidence of secondary factors, also known as objective indicia of nonobviousness." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)) (internal numbering omitted). Objective indicia of non-obviousness include the commercial success of the invention, the invention's satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham*, 383 U.S. at 17.

As mentioned, a patent will be invalid if the invention was both "ready for patenting" and the subject of a commercial offer for sale more than one year before the patent application was filed. *See* 35 U.S.C. § 102(b); *Pfaff*, 525 U.S. at 67. This is known as the "on-sale bar." An invention is "ready for patenting" if it has been reduced to practice, meaning actually made, or if it has been sufficiently described or depicted in drawings by the inventor to enable a person skilled in the art to make the invention. *See In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1373 (Fed. Cir. 2008). A commercial offer for sale occurs where the invention is marketed commercially. *Pfaff*, 525 U.S. at 67. This includes both

actual sales of the invention and offers to sell the invention. *Hamilton Beach Brands, Inc. v. Sunbeam Products, Inc.*, 726 F.3d 1370, 1374 (Fed. Cir. 2013). However, a commercial sale does not occur where the transaction is for experimental purposes. *Pfaff*, 525 U.S. at 67. The transaction will be for experimental purposes if represents a "'bona fide effort to bring the invention to perfection, or to ascertain whether it will answer the purpose intended,'" rather than represent an effort to earn profits. *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 998 (Fed. Cir. 2007) (*quoting City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 136 (1877)).

A patent must also meet the requirements of 35 U.S.C. § 112, which requires the specification to contain a sufficient description of the invention, to enable make and use of the invention, and to be sufficiently definite. *See* 35 U.S.C. § 112(a)–(b). A specification has a sufficient written description if it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" of the patent application. *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011). The enablement requirement is satisfied if the specification allows a person of ordinary skill in the art to make and use the invention without undue experimentation. 35 U.S.C. § 112 (a); *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). Finally, "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*,

134 S. Ct. 2120, 2124 (2014).

1. Whether the Asserted Claims of the '122 and '216 Patents are Invalid.

Defendants argue that the asserted claims of the '122 and '216 patents are invalid for three reasons. First, they argue that the patents are invalid as obvious in light of the prior art at the time of the invention, October 15, 2001. Second, they argue that the '122 and '216 patents are invalid under the on-sale bar because they were ready for patenting and the subject of a commercial offer for sale more than a year before the patent applications were filed. Third, they argue that the patents fail to satisfy the written description, enablement, and definiteness requirements of 35 U.S.C. § 112.

a. Whether Endo's Invention Would Have Been Obvious to a Person of Ordinary Skill in the Art.

Defendants argue that Endo's invention, embodied in the asserted claims of the '122 and '216 patents, would have been obvious to a person of ordinary skill in the art at the time the patent applications were filed. There was general consensus at trial regarding the definition of a person of ordinary skill in the art in 2001. The parties agreed that such a person would have "at least a master's degree or a doctorate in pharmaceutical sciences with experience in developing formulations, including controlled release formulations. If the individual had a lesser degree of training, such as a bachelor's degree, then he would need several more years of experience in the areas of pharmaceutical formulation development." Trial Tr. at 1502:13–20.

This is where the parties' consensus ended. In all, the parties highlight

four areas in dispute regarding the obviousness/non-obviousness of Endo's invention[17]: (i) whether there was a motivation to select oxymorphone for use in a controlled-release delivery system; (ii) whether the prior art discloses the dissolution ranges claimed in the '122 and '216 patents; (iii) whether the pharmacokinetic limitations of the patent claims are obvious or otherwise invalid; and (iv) whether secondary factors indicate the invention's non-obviousness.

i. Whether There Was a Motivation to Select Oxymorphone For Use in a Controlled Release Setting.

The first area of dispute with regard to obviousness of the '122 and '216 patents is whether an ordinarily skilled artisan would be motivated to select oxymorphone for use in a controlled release setting.

Oxymorphone was known at the time of the invention. At trial, Dr. Banakar explained that opioids, as a family of molecules, have long been known in the art for their analgesic effect. *See* Trial Tr. at 1460. Oxymorphone specifically was known, and in fact had been approved and marketed under the branded name Numorphan between 1959 and 1971. Trial Tr. at 2623:17–21. Numorphan would be known to a person of ordinary skill in the art in 2001 because it had been included in the Physician's Desk Reference as early as 1969. *See* Physician's Desk Reference, Twenty-Third Edition (1969) at 698 (DTX-2890) (describing "Numorphan (oxymorphone) hydrochloride [as] a semisynethetic

[17] Endo stipulated to the disclosure in the art of hydrophilic and hydrophobic materials, gelling agents, matrix formation, and other disclosures. *See* Stipulation and Order at 2–3, No. 12-CV-8060 (Mar. 27, 2015) (Dkt. #152).

narcotic . . . indicated for all instances of pain . . . [administered] Orally . . . every 4 to 6 hours."). But while Numorphan was known in the art, it was also understood to be an immediate-release drug, to be taken every four to six hours. Trial Tr. at 1458:13–15. Endo had also been selling oxymorphone in intravenous and suppository forms, both of which are immediate release formulations. *See* Trial Tr. at 247–48, 450:7–9.

Although oxymorphone was known for use in immediate release form, it had never been integrated into a controlled release setting. This is not surprising given the state of the art in 2001.

Controlled release platforms were themselves known to persons of ordinary skill in the art at the time. Trial Tr. at 1474–75. For example, a patent awarded in 1997, Number 5,662,933 (the "Baichwal Reference") taught the use of the TIMERx system, the same system Endo licensed from Penwest, with a "wide variety" of active ingredients, including the analgesics aspirin, codeine, morphine, dihydromorphone, and oxycodone. *See* Baichwal Reference at 8:29–30 (DTX-3559). Moreover, the 1999 Physician's Desk Reference listed two controlled release opioid tablets, MS Contin and OxyContin, both of which used hydrophilic delivery systems. *See* Physician's Desk Reference at 2556, 2569–79, Fifty-Third Edition (1999) (DTX 2870 and DTX 2961); *see also* Trial Tr. at 1476. However, while these pieces of art taught the integration of some opioids in a controlled release setting, they were silent in regard to integrating *oxymorphone* into a controlled release setting.

The teaching of the prior art indicates that selecting oxymorphone for use

in a controlled release setting would have been counterintuitive because of its exceptionally low bioavailability. As plaintiffs' expert Dr. Salomon Stavchansky testified, bioavailability refers to the amount of drug that survives metabolism in the liver and gut and enters the bloodstream, where it will be available to provide a therapeutic effect. *See* Trial Tr. at 2608–09. The 2000 Physician's Desk Reference reported the bioavailability of oxycodone at 60–87% and morphine at 40%. *See* Physician' Desk Reference at 2527, 2537, 54th Edition (2000) (PTX-404 and PTX-0532). Hydromorphone had a bioavailability of between 20% and 60% depending on the source. *Compare* Sarhill *et al.*, *Hydromorphone: pharmacology and clinical applications in cancer patients* at 86 (2000) (DX-3157) *with* Ritschel and Kearns, *Handbook of Basic Pharmacokinetics* at 491 (5th ed. 1998) (PTX-509). Oxymorphone had a reported bioavailability of just 10%. *See* Gordon *et al.*, Opioid Equianalgesic Calculations, 2 J. Palliative Med at 212 (1999) (PTX-117).

The art available in 2001 taught that bioavailability is a significant, even crucial, factor in evaluating a drug's suitability for placement in a controlled release vehicle. *See* U.S. Patent Number 5,958,452 (the "Oshlack Reference") at 2:47–50 (DTX-3560) ("[D]issolution time and . . . bioavailability . . . are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions."). This is because bioavailability was suspected to influence a drug's inter-subject variability, meaning the differences in its clinical effect among a group of patients. *See* Hellriegel et al., *Interpatient variability is related to the extent of absorption*, 60 Clinical Pharmac. & Therap.

at 604 (1996) (PTX-461) ("Our results clearly show a significant relationship between the absolute bioavailability of an oral dosage form and its intersubject . . . variation"). The lower a drug's bioavailability, the more likely the drug will be to produce variations in clinical effect among a group of patients. *Id.*; *see also* Trial Tr. at 26:20–24. This effect on intersubject variability was suspected to be more pronounced given other influences, including a patient's food consumption and amount of restedness. *See* William H. Barr, *Bioavailability of Oral Solid Dosage Forms and Clinical Response to Drug Therapy* at 58-59 (1973) (PTX-412).

As a result of its exceptionally low bioavailability, oxymorphone was considered by those skilled in the art to be a poor candidate for controlled-release treatment. Indeed, in an article in the Journal of Pharmaceutical Sciences, a group of authors explained that oxymorphone is ideally suited for delivery through the skin since it "is not very effective orally." *See* Aungst *et al.*, *Transdermal Oxymorphone Formulation Development and Methods for Evaluating Flux and Lag Times for Two Skin Permeation-Enhancing Vehicles*, 79 J. Pharmac. Sciences at 1072 (PTX-410). Moreover, the art taught that because drugs like oxymorphone are almost wholly metabolized upon first passing through the liver, the only way to increase the amount of drug that survives to the bloodstream is to use an exceptionally large dose from the beginning, potentially "risking toxicity." Read *et al.*, *Gastrointestinal Dynamics and Pharmacology for the Optimum Design of Controlled-Release Oral Dosage Forms*, 4 CRC Critical Reviews in Therap. Drug Carrier Systems 221, 240 (PTX-505).

Controlled release delivery systems were suspected of actually reducing

certain drugs' bioavailability due to a phenomenon known as "saturable first pass metabolism." Trial Tr. at 2640. Some drugs, when administered in immediate release form, "saturate" or exhaust the liver's metabolizing enzymes, allowing the remainder of the drug to enter the bloodstream unopposed. *See* Welling & Dobrinska, *Dosing Considerations and Bioavailability Assessment of Controlled Drug Delivery Systems* at 258 (1986) (PTX-526). Controlled release drugs, because they release the active ingredient slowly, may never "saturate" the liver's defensive enzymes, and will thus be blocked far more efficiently than their immediate release counterpart. *Id.*; *see also* Mordenti and Williams, *Controlled Release Drug Delivery: Pharmacodynamic Consequences* at 208–09 (1988) (PTX-491) ("controlled release formulations have less of a tendency to produce saturable first pass metabolism . . . ."). To a person of ordinary skill in the art, the saturable first pass phenomenon would have, at least to some degree, cautioned against selecting oxymorphone, a low-bioavailability opioid, for controlled-release treatment.

The notion that low-bioavailability drugs were considered unsuitable for extended-release formulation is reinforced by the fact that, until Endo's development of OPANA®ER, there were remarkably few such examples. At trial, Endo and its experts repeatedly emphasized that at the time of its invention, OPANA®ER was the lowest-bioavailability drug, by a wide margin, ever formulated into a controlled-release setting. *See, e.g.,* Trial Tr. at 2655-56, *see also* Plaintiff's Opening Statement Slide Deck at 001.92 ("Why Oxymorphone? . . . Lower bioavailability than any prior controlled release formulation."). During

cross-examination of Endo's expert Dr. Stavchansky, defendants revealed that another low-bioavailability drug, oxybutynin (bioavailability of 6%), had previously been developed into a controlled release formulation. *See* Trial Tr. 2779. But in the court's view, this merely served to underscore, rather than diminish, the fact that low bioavailability drugs were remarkably rare in controlled-release settings. Dr. Stavchansky's unmistakable surprise upon being confronted with Oxybutynin's low bioavailability, and its total absence from the expert reports of both sides, impressed on the court that low-bioavailability drugs were, at the time of the invention, perceived as unsuited for development into controlled release forms.

Defendants argue that, rather than teach away from the selection of oxymorphone, the prior art actually discloses its use in the type of controlled-release setting embodied in the '122 and '216 patents. The first of these pieces of prior art is an application for an international patent application filed in 2000. *See* PCT International Publication No. WO 01-09661 A2 (the "Maloney Reference") (DTX-3561). The second piece of prior art is United States Patent Number 5,958,452 (the "Oshlack Reference") (DTX-3560).

The Maloney Reference describes a sustained-release formulation for opioid compounds that avoids the need for certain product features hitherto common in sustained release formulations. *See* Maloney Reference at 8. In describing this invention, Maloney clearly discloses the type of controlled-release matrix delivery systems asserted in Claim 1 of the '122 Patent and claims '72 and '77 of the '216 Patent. *See* Maloney Reference at 6–7, 9. However, the

Maloney reference claims as its invention "an improved formulation for the sustained release of *oxycodone*," not oxymorphone. *Id.* at 7 (emphasis added). Indeed, each of the many examples provided in the Maloney Reference deal exclusively with oxycodone hydrochloride, *id.* at 15–17, a completely different opiate from that embodied in the '122 and '216 patents.

The Maloney Reference does mention the use of oxymorphone. However, it does so by sheer overinclusion, by simply listing dozens of molecules and purporting to cover them as part of the invention. First, Maloney discloses controlled release dosage forms combined with an "opioid compound." *Id.* at 8. This opioid compound is defined to preferably include *all* opioid analgesics, meaning the "diverse group of drugs . . . that displays opium or morphine-like properties." *Id.* at 9. Maloney then goes further, providing a list of 65 molecules considered to be opioid analgesics. *Id.*; *see also* Trial Tr. at 1671. This list includes oxymorphone. Maloney at 9. It also includes heroin, opium, and fentanyl. *Id.*

The court finds it difficult to believe that a person of ordinary skill in the art, upon reading Maloney, would understand oxymorphone to be suitable for a controlled release setting. Maloney's vast listing of molecules, inclusion of heroin, opium, and fentanyl, raises doubts as to whether that list would be taken seriously as indicating suitability for controlled release treatment. *See* Trial Tr. at 1671; *see also* Maloney at 8–9 ("Preferably the opioid compound included in the formulation is an opioid analgesic . . . . Opioid analgesics include . . . heroin . . . opium . . . etc . . . ."). Indeed, fentanyl was widely understood as only suitable

for transdermal, not oral, delivery. Trial Tr. at 1672. In all, Maloney mentions oxymorphone four times. *See* Maloney Reference at 9, 13, 26, 28. However, in each instance where oxymorphone is mentioned, it is situated among dozens of molecules, such as fentanyl, whose suitability for inclusion in a controlled-release setting is not established in the reference. *Id.*

Maloney is also silent as to the dosing interval of the invention. A primary feature of Endo's invention, embodied in the first claims of both the '122 and '216 patents, is that Endo's tablet will be suitable for a 12 hour dosing interval, meaning the patient will only have to take the tablet twice per day. *See* '122 Patent at 25:50–53; '216 Patent at 26:52–53. Maloney does provide dissolution data for oxycodone hydrochloride, but for reasons that will be discussed below, this data was measured using methods that would not give any indication of the *in vitro* dissolution rate of oxymorphone, which Endo was the first to measure and which it claimed in its patents. *See* Maloney Reference at 21. A person of ordinary skill in the art, upon reading Maloney, would have no understanding of the dosing interval of controlled-release oxymorphone.

The Oshlack Reference shares the Maloney Reference's deficiencies, and adds its own. The Oshlack reference describes using "melt extrusion technology" to produce sustained-release dosage forms, where such technology had previously been used only for immediate release formulation. Oshlack Reference at 1:10–15. Like Maloney, Oshlack discloses the use of "sustained-release matrix pharmaceutical formulations." *Id.* However, it only discloses the use of hydrophobic delivery systems, not hydrophilic systems. Oshlack Reference at

3:39–49; 6:44. In describing suitable active ingredients, Oshlack includes opioid analgesics, but like Maloney, simply lists 72 molecules as covered without regard as to whether they would actually be suitable for use in a controlled release setting. *Id.* at 8-39. Indeed, Oshlack includes heroin, opium, and fentanyl as suitable opioid analgesics. *Id.* But just as with Maloney, it is doubtful that these active ingredients would be understood as capable of being housed in a controlled release delivery system. *See also* Trial Tr. at 1671–72 ("There is no controlled release oral formulation of fentanyl available, but there is a controlled release dermal formulation which is applied on the skin.").

While Oshlack contains examples providing dissolution data for certain active ingredients, it only does so for chlorpheniramine, morphine, oxycodone, hydromorphone, dilaudid, tramadol, and stearyl alcohol. Oshlack Reference at 14–25. It does not list a single example using oxymorphone. This is notable because, as discussed, oxymorphone has a much lower bioavailability than any of the opioids listed as examples. Beside listing oxymorphone among other potential active ingredients, *see, e.g.*, Oshlack at 7:37–38, Oshlack simply gives no indication, to a person of ordinary skill in the art, that the opioid could actually be integrated into a controlled release setting, much less a setting providing a 12 hour dosing interval.

The court is persuaded by the expert testimony that the art taught away from the selection of oxymorphone for use in a controlled release setting because of its exceptionally low bioavailability. Defendants failed to show that a person of ordinary skill in the art would, upon reading the Maloney, Oshlack, and other

prior art references, be motivated to select oxymorphone for development into a controlled release formulation.

ii. Whether the Prior Art Discloses the Claimed Dissolution Rates.

As discussed above, the prior art in 2001 taught away from the selection of oxymorphone for use in a controlled release setting. But even if an artisan were motivated to select oxymorphone, a key feature of Endo's invention is the pairing of oxymorphone with a controlled-release delivery system which releases the active ingredient at a specified rate. *See, e.g.*, '122 Patent 25:55–60. Three of the four claims asserted from the '122 Patent contain dissolution limitations. *See* claims 2, 3, and 19; '122 Patent at 25–28. Likewise, nineteen of the twenty asserted claims from the '216 Patent recite (directly or by reference) dissolution limitations. *See* claims 22, 40 and 42,[18] 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, 82. '216 Patent at 26–34. Thus, crucial to defendants' assertion of obviousness is whether the prior art discloses to a person of ordinary skill the dissolution ranges recited in the '122 and '216 patents.

This creates two problems for defendants' obviousness argument. First, each of the prior art references relied on by defendants discloses the dissolution profile of a drug with an active ingredient other than oxymorphone. *See* Oshlack Reference at 18–19 (oxycodone); Baichwal Reference at 15:32–40 (albuterol); Maloney Reference at 23 (oxycodone). Second, most of the prior art references defendants relied on used different methods to test dissolution than that used

[18] Although mentioned here, the court makes no conclusions regarding the validity of claims 40 and 42 of the '216 Patent because defendants do not infringe those two claims.

in the '122 and '216 patents. *Compare* Maloney Reference at 23 (using the USP Basket Method at 100 revolutions per minute) *with* '122 Patent at 26:65–68 (using the USP Paddle Method at 50 revolutions per minute).

To demonstrate the obviousness of Endo's dissolution claims, it was incumbent on defendants to show two things at trial: (1) that a person of ordinary skill, upon reading the prior art, would understand oxymorphone to be interchangeable with other active ingredients in a controlled release delivery system; and (2) that the results of the dissolution testing methods used in the prior art could be read to indicate the results of the dissolution testing methods used in the Endo patents.

1. A Person of Ordinary Skill in the Art Would Not Understand Oxymorphone to Be Interchangeable With Other Active Ingredients in the TIMERx System.

At trial, Dr. Banakar testified that the TIMERx system Endo licensed from Penwest was essentially "plug and play," meaning that one could take Penwest's controlled-release delivery system and easily insert various suitable active ingredients. Trial Tr. at 1516:21–22. ("Now they plug and play, they changed the drug and put another drug and provide the system that I am looking for."). Referring to Penwest's 1997 filing with the Securities and Exchange Commission, Dr. Banakar noted that various drug substances had been paired with TIMERx, including the heart drug Nifedipine and, pursuant to Endo's development work, oxymorphone. Trial Tr. at 1519:7–25. In Dr. Banakar's opinion, different active ingredients may be readily interchanged in the TIMERx system. Trial Tr. at 1522–23 ("Baichwal discloses . . . the TIMERx platform using gums. Baichwal also

discloses analgesics which could be put into these gums to get controlled release formulations for morphine . . . . A person of ordinary skill in the art would be able to develop a controlled release formulation for oxymorphone using the same technology as Baichwal discussed."). Thus, in his view a person of ordinary skill in the art, upon learning that other molecules had been paired with TIMERx, would find it obvious to do the same with oxymorphone.

Plaintiffs' expert on non-obviousness, Dr. Stavchansky, disagreed with Dr. Banakar's characterization of the TIMERx technology as a "plug and play" system. *See* Trial. Tr. at 2680:4–5. Dr. Stavchansky noted that different opioid molecules have different pharmacokinetic effects, and the fact that one opioid has been integrated into a controlled release setting does not indicate similar success for a different opioid. *Id.* at 2681. It is only upon testing the new opioid in the controlled-release setting under both laboratory conditions and in live subjects that one can assess its compatibility with the TIMERx system. *See id.* To support this opinion, Dr. Stavchansky compared two controlled release drugs marketed by Purdue Pharma, MS Contin (morphine) and OxyContin (oxycodone), and discovered that even though both use the same controlled-release technology, they exhibit significantly different formulations. Trial Tr. at 2686–88. This indicates that it is no simple matter to "plug" a new active ingredient into a previously used delivery system.

The court finds Dr. Stavchansky to be more persuasive than Dr. Banakar on this issue. The court is not persuaded that controlled release systems, including TIMERx, would be understood by artisans as simply "plug and play."

This is because, as Dr. Stavchansky testified, each controlled release drug is independently formulated and tested. A person of ordinary skill in the art, upon learning that one opioid had been developed into a controlled release formulation, would not find it obvious to do the same with oxymorphone.

2. Dissolution Profiles Measured Using the USP Basket Method and Paddle Method at 100rpm Were Not Known to Teach Dissolution Profiles Measured Using the USP Paddle Method at 50rpm.

Even if the court were to accept defendants' argument regarding the interchangeability of oxymorphone and other active ingredients in controlled release systems such as TIMERx, the prior art would still fail to teach Endo's claimed dissolution ranges. Since OPANA®ER was the first drug to integrate oxymorphone into a controlled release setting, all of the prior art references disclose the dissolution rates of *other* controlled release drugs such as albuterol and oxycodone. *See, e.g.*, Baichwal Reference at 14:36-41 (showing dissolution for albuterol, a non-opioid). The person of ordinary skill in the art would have to assume that the disclosed dissolution rate of drugs such as albuterol and oxycodone would somehow be indicative of the dissolution rate Endo claimed for controlled-release oxymorphone.

But even if the artisan were to make this assumption, which the court is not convinced is reasonable, he would have to appreciate some way to correlate the dissolution profiles of the non-oxymorphone controlled release drug to the dissolution profile of controlled-release oxymorphone. This presents a significant challenge to defendants' obviousness argument, because most of the prior art

references measured dissolution using different testing methods than what Endo used in its dissolution claims.

The Endo patents express the dissolution profile for controlled-release oxymorphone using the USP Paddle Method at 50rpm. *See* '122 Patent at 25:57. Where, for example, the Endo patents say that a tablet releases 45% to 80% of the active ingredient within four hours, they mean four hours after being placed in a vessel containing 500ml of medium that is agitated by the spinning of paddle-shaped blades at fifty revolutions per minute. *See supra* Part A(1)(a).

Most of the prior art references defendants rely on measured dissolution in a different way. The Maloney Reference measured dissolution of controlled-release oxycodone using the USP Basket Method at 100rpm. *See* Maloney Reference at 23. The same is true of another reference, United States Patent Number 5,549,912 (the "'912 Patent"). *See* '912 Patent at 2:20–25 (DTX-0042). The Oshlack Reference measured dissolution using the Paddle Method, but did so at twice the speed as Endo, 100 revolutions per minute, and in nearly twice the aqueous buffer (900ml compared to Endo's 500ml of media). *See* Oshlack Reference at 11:66.

While Maloney and Oshlack measured dissolution differently than Endo, some of their dissolution ranges coincide with those claimed for oxymorphone in the '122 and '216 patents. For example, the Maloney Reference shows that certain oxycodone hydrochloride tablets will be 25% dissolved at one hour. *Id.* The Oshlack Reference shows dissolution of 12.5% to 42.5% at one hour. *See* Oshlack Reference at 12:24–27. Both are similar to the dissolution range Endo

claimed for oxymorphone, 15% to 50% at one hour. *See* '122 Patent at 25:57–60.

But to accept that Oshlack, Maloney, and the '912 Patent taught the dissolution ranges claimed in the '122 and '216 patents, the court would have to accept that a person of ordinary skill in the art would understand some correlation between results obtained using the Paddle and Basket methods at different speeds.

Dr. Banakar suggested that two pieces of art, the Hanson Reference and the Madden Reference, taught such a relationship between the two methods. Trial Tr. at 1551–52. The "Hanson Reference" is a handbook on dissolution testing published in 1991. *See* William A. Hanson, *Handbook of Dissolution Testing* (2d Ed. 1991) (DTX-3556). It provides that "for general purposes when not otherwise specified—rates of 50 rpm for the paddle and 100 rpm for the basket are recommended and have proved to be *roughly equivalent* to one another in producing dissolution." *Id.* at 36 (emphasis added). Similarly, in a 1998 report presented to the American Association of Pharmaceutical Scientists, a group of authors observed that the four USP dissolution testing methods, including the Paddle and Basket Methods, produce similar dissolution profiles "regardless of the degree of agitation . . . ." *See* Madden *et al.*, *Impact of Apparatus Type and Hydrodynamics on the Release of a Highly Soluble Drug From a Hydrophilic Matrix Tablet* (the "Madden Reference") (DTX-0069 at 9956).

However, a significant body of other art showed no such relationship. A textbook published in 1999 stated that:

"the use of various testing methods makes it even more difficult to

> interpret dissolution results because there is no simple correlation among dissolution results obtained with various methods. For many drug products, the dissolution rates are higher with the paddle method . . . . No simple correlation can be made for dissolution results obtained with different methods."

Shargel and Yu, *Applied Biopharmaceutics & Pharmacokinetics* at 145 (1999) (PTX 637) (the "Shargel Reference"). Similarly, a book written by defendants' own expert, Dr. Banakar, stated that the dissolution testing device used is one of six factors influencing dissolution rate. *See* Umesh Banakar, *Pharmaceutical Dissolution Testing* at 133–34 (PTX-411) (the "Banakar Reference"). Finally, an article published in 1978, the Hardwidge Reference, taught that different dissolution testing methods produce different results depending on the speed of agitation. *See* E.A. Hardwidge *et al.*, *Comparison of Operation Characteristics of Different Dissolution Testing Systems*, 67 J. Pharmaceutical Sciences 1732 (1978) (PTX-0458) (the "Hardwidge Reference"). Hardwidge shows that the Paddle Method at 100rpms produces significantly faster dissolution over time than the Paddle Method at 50rpm. *See* Hardwidge Reference Fig. 1. Moreover, when dissolution is tested for the Paddle and Basket Methods at the same speed of agitation, the Paddle Method will produce faster dissolution results. *Compare id.* Fig. 1 *with id.* Fig. 2.

Even accepting, without approving, defendants' argument that a person of ordinary skill in the art would understand the dissolution profiles for the controlled release formulation of one molecule as teaching the dissolution profile

for the controlled release formulation of a wholly different molecule,[19] the court remains unpersuaded that the art in 2001 taught the interchangeability of the USP Paddle Method and USP Basket Method at different speeds. At most the Hanson Reference merely provided that the two methods were "roughly equivalent in producing dissolution." This would be woefully insufficient instruction to a person of ordinary skill in the art, and would provide no way to infer some correlation between dissolution results obtained using the different methods. Rather than teach the equivalency of the various USP testing methods, a significant body prior art, including the Shargel, Banakar, and Hardwidge references, taught that dissolution results from one testing method were non-interchangeable with results obtained from a different testing method.

The court concludes that defendants have failed to show disclosure in the art of the dissolution limitations claimed in the '122 and '216 patents. The court is unpersuaded that a person of ordinary skill in the art would understand oxymorphone to be interchangeable with oxycodone, morphine, and albuterol in a controlled release setting, nor is it clear that he would understand dissolution values for those drugs as indicating the dissolution profile of controlled-release

[19] The court is willing to accept this assumption only to a certain point. Two prior art references use the Paddle Method at 50rpm but nonetheless fail to disclose the claimed ranges for other reasons. The Baichwal Reference shows the dissolution profile of albuterol, which isn't an opioid. *See* Baichwal Reference at 14:36-41 (using the Paddle Method at 50rpm). The court is unwilling, given the defendants' high burden, to go so far as to accept that the dissolution of a non-opioid would indicate to an artisan the dissolution of oxymorphone. A 1999 article shows the dissolution profile of an opioid, morphine sulfate, measured using the Paddle Method at 50rpm. *See* Webster *et al.*, *In Vitro Studies on the Release of Morphine Sulfate From Compounded Slow-Release Morphine-Sulfate Capsules* at 3, Int'l J. Pharmaceutical Compounding (1999) (the "Webster Reference") (DTX-0028). But while morphine is an opioid, the article provides dissolution values falling outside of those later claimed by Endo for oxymorphone. *Compare* Webster Reference at Fig. 2 (showing dissolution of morphine sulfate of ~80% at four hours) *with* '216 Patent at 34:36-40 (showing dissolution of oxymorphone of 58-66% at four hours).

oxymorphone. Even if a person of ordinary skill in the art made this assumption, the dissolution data provided in prior art would not predict or indicate Endo's claimed ranges because it was obtained using different testing methods. Because there was no way to equate the results obtained from the different testing methods, a person of ordinary skill in the art would not have been able to extrapolate from the prior art the dissolution limitations claimed in the '122 and '216 patents.

iii. Whether the Claimed Pharmacokinetic Limitations are Obvious or Otherwise Invalid.

In addition to the dissolution limitations discussed above, the '122 and '216 patents also recite pharmacokinetic limitations, or limitations describing how Endo's tablets will affect the human body once ingested. The pharmacokinetic limitations of the patents can be grouped into four broad categories: "analgesic effect" limitations (providing that the tablet will provide pain relief for a certain period of time); "food effect" limitations (limitations describing blood concentration levels after having eaten a meal as opposed to having fasted); metabolite limitations (limitations stating that ingesting the tablets will produce the metabolite 6-OH oxymorphone); and peak plasma level limitations (limitations describing when and how often patients' blood will exhibit peak concentrations of oxymorphone). *See, e.g.*, '216 Patent at 26:35–55; *see also supra* parts (A)(1)(a)–(b).

Defendants challenged the validity of the asserted pharmacokinetic limitations at trial, arguing that: (1) some of the asserted pharmacokinetic limitations are the result of natural phenomena and therefore not patentable; (2)

even if those pharmacokinetic limitations are patentable, they were nonetheless obvious in light of the prior art; and (3) the claimed pharmacokinetic limitations could have been predicted by a convolution analysis. The court will address each of these arguments in turn.

1. The Claimed Pharmacokinetic Limitations Do Not Merely Recite Natural Phenomena.

Defendants argue that some of the pharmacokinetic limitations claimed in the '122 and '216 patents merely capture natural phenomena and are therefore ineligible for patent protection. *See* Trial Tr. at 177:6.

Many of the asserted claims capture what are known as "food effects," meaning they provide that concentrations of oxymorphone or its metabolite in the bloodstream will vary to a certain extent depending on whether a patient has eaten or fasted. For example, claims 20 of the '122 Patent and 40 of the '216 Patent provide that total blood concentrations of oxymorphone ($AUC_{(0\text{-}inf)}$) will be no more than 20% higher when the tablet is taken after having eaten a meal as opposed to having fasted; and that maximum observed concentrations of oxymorphone (C_{max}) will be no more than 50% higher after having eaten. *See* '122 Patent at 26:54–58; '216 Patent at 30:10–12 (depending from Claim 38).

Other limitations of the patents describe "peaks," or highpoints, of oxymorphone concentration in the blood occurring within one to eight hours, and then recurring once or twice more within twelve hours. *See, e.g.*, '216 Patent at 26:35–55. Finally, some of the claims provide that the formulation will provide detectable levels of oxymorphone and its metabolite 6-OH oxymorphone, and in

certain ratios. *See id.*

At trial, Dr. Banakar testified that the food effect, peak concentration, and "detectable level" limitations of the '122 and '216 patents are the result of the body's natural processes, and would be exhibited whenever oxymorphone is administered to human subjects. *See, e.g.*, Trial Tr. at 1571:17–24. With regard to the food effect limitations, Dr. Banakar testified that Endo merely administered controlled-release oxymorphone to subjects and then claimed the resulting blood concentrations. Trial Tr. at 1572:7–11. For example, Dr. Banakar claimed that Endo performed a food effect study in subjects which showed total blood concentration (AUC) of oxymorphone to be 18% higher after having eaten a meal as compared to having fasted, and simply recited as a claim limitation AUC values of not greater than 20%. Trial Tr. at 1572. Endo purportedly used a similar strategy in reciting the claim limitations for maximum observed concentrations of oxymorphone (C_{max}). *Id.*

At trial, defendants' expert failed to cite any reference for the proposition that the food effect limitations merely capture natural phenomena, other than opining to that effect. *See* Trial Tr. at 1501:21-25, 1571:13-16. Dr. Banakar offered no other support for his view that the pharmacokinetic limitations are the result of the body's natural processes. Of course, the court gives considerable weight to Dr. Banakar's opinion given his clear expertise in the field. But the court finds his testimony to be undermined by the fact that oxymorphone, when administered in an immediate release formulation, produces a total blood concentration (AUC) of 30% under fed conditions. Trial Tr. at 484:6–9; '122

Patent at 10:18–20. This is considerably higher than the food effect of controlled release oxymorphone, which when taken under fed conditions produces total blood concentration (AUC) of 20%. Trial Tr. at 486:9–14. If the food effect of oxymorphone was merely a result of natural processes, then one would expect the same total blood concentration (AUC) after eating for both the immediate release and controlled release formulations. This is not the case. Rather, it appears that formulating oxymorphone into a controlled-release setting curbs the pronounced food effects exhibited by immediate release oxymorphone, reducing them to more tolerable levels. *Cf.* Trial Tr. at 487–88. It is the inventive dosage form, and not merely the body's metabolism, that provides the significant reduction in food effects claimed in the Endo patents.

The invention has an equally significant effect on the number of peaks in oxymorphone blood concentration levels. When immediate release oxymorphone is ingested, the subject's blood exhibits a single dramatic peak in blood concentration levels occurring in the first four hours, and a second, much smaller peak occurring at about twelve hours. *See* '122 Patent at Fig. 5. When controlled-release oxymorphone is ingested, the subject's blood exhibits three moderate peaks in blood concentration levels over about twelve hours. *Id.* The highest peak occurs within eight hours. *Id.* Endo claimed these multiple-peak and highest-peak effects as limitations in the '216 Patent. *See, e.g.*, '216 Patent cls. 1, 78.

At trial, Dr. Banakar opined that the "multiple" peaks exhibited by controlled release oxymorphone were the result of a natural process known as

"enterohepatic recirculation." Enterohepatic recirculation means that once ingested, oxymorphone is circulated between the intestine, liver, and bile duct multiple times, resulting in multiple peaks in blood concentration levels. See Trial Tr. at 1495. Indeed, in correspondence Endo submitted to the FDA in 2002, Endo explained that "the presence of multiple peaks . . . suggests the presence of enterohepatic recycling . . . ." Study of Human Pharmacokinetics and Bioavailability Data (Nov. 14, 2002) (DTX-1444 at 4173). Thus, it is Dr. Banakar's opinion that the multiple-peak limitations of the asserted claims merely describe the natural phenomena of enterohepatic recirculation of oxymorphone.

Dr. Banakar's observation appears sound, but the conclusion he draws is not. The "multiple peaks" that occur following administration of controlled release oxymorphone are of course the result of the body's natural processes. It could be no other way. But Endo's patents do not pretend to claim the natural process of enterohepatic recirculation. Rather, the Endo patents claim a dosage form for oxymorphone that provides an analgesic effect over twelve hours, *see* '122 Patent at 25:50–52, and which causes multiple peaks in blood concentration levels (and ensuing continued analgesic effectiveness) during that same period. '216 Patent at 34:20–24. Similarly, Endo claimed that that blood levels will peak within 8 hours of administration, *id.* cl. 1, as opposed to within 4 hours as would be expected with immediate release oxymorphone.

These pharmacokinetic effects *are only possible* because the dosage form, the invention itself, slows the release of oxymorphone to such a degree that: (1)

peak blood concentration of oxymorphone occurs later (within 1–8 hours) than with immediate release oxymorphone (within 1–4 hours); and (2) the body has multiple opportunities to recirculate the opioid through the bile duct, liver and intestines, producing multiple high-points in blood concentration levels. This multiple peaking is not possible with immediate release oxymorphone because the drug simply does not remain concentrated in the body long enough to be circulated multiple times and produce multiple peaks. Thus, the peak limitations of the '216 Patent do not merely recite natural processes, but instead recite the unnatural result of the body's prolonged exposure to oxymorphone, made possible only because of the inventiveness of the dosage form.

Dr. Banakar also challenged the metabolite limitations of the asserted claims. As discussed in the claim construction section of this decision, the asserted claims of the '216 Patent contain limitations stating that the formulation will "provide[] detectable blood plasma levels of 6-OH oxymorphone [the metabolite] and oxymorphone," and that ratio of 6-hydroxy-oxymorphone [the metabolite] to oxymorphone in the bloodstream will be between about 0.5 to 1.5. *See, e.g.*, '216 Patent cls. 1, 42, 62 and 64 (incorporating Claim 55). Dr. Banakar argued that these limitations merely recite the inevitable—that once oxymorphone is administered to a patient, that patient's blood will invariably exhibit detectable levels of oxymorphone *and* its metabolite, and always within the ratio claimed. *See* Trial Tr. at 1594:20–23. Thus, Dr. Banakar asserts that the metabolite limitations merely record natural processes. *Id.* at 1594–95.

Again, the court believes that Dr. Banakar's conclusion is unsound. It goes

without saying that the liver's ability to metabolize substances is a natural process. But Endo did not attempt to patent the operation of the human liver, much less the operation of the liver on a natural substance. Rather, Endo patented the myriad of pharmacokinetic effects that occur when a subject ingests the inventive formulation of the semi-synthetic opioid oxymorphone in a controlled-release delivery system. These effects do not occur in the absence of the controlled-release dosage form constituting the invention, and are therefore not natural phenomena.

2. The Pharmacokinetic Limitations Were Not Otherwise Disclosed in the Prior Art.

Defendants argue that even if the pharmacokinetic limitations are not invalid as claiming natural phenomena, they are nonetheless disclosed in the prior art. Defendants assert numerous pieces of prior art to this effect: the Maloney Reference, the Oshlack Reference, the Baichwal Reference, the '912 Patent, the Penwest Reference, and an article published in 2000 in the journal "Cancer Control." *See* James F. Cleary, *Cancer Pain Management*, 7 Cancer Control 120 (Mar. 2000) (DTX-1951) (the "Cleary Reference"). The court must determine whether these references teach the pharmacokinetic characteristics for oxymorphone claimed in the '122 and '216 patents.

The first pharmacokinetic limitation of the asserted claims is that the dosage form containing oxymorphone or its salt will prove analgesically effective, meaning provide a painkilling effect, for twelve hours. *See* '122 Patent at cl. 1; '216 Patent cl. 1(iv); *see also supra* Part A(1)(a)–(b).

None of the prior art references taught the analgesic effectiveness of

oxymorphone over a twelve-hour period. Maloney taught the analgesic effectiveness of a different molecule, oxycodone, but gave no indication of oxycodone's dosing interval. *See generally* Maloney Reference. Maloney did list the *in vitro* dissolution rate for oxycodone over twelve hours, *id.* at Table 2, and from this it is possible that a person of ordinary skill in the art could infer that oxycodone would have sustained analgesic effects given that much of the drug remained undissolved during that period. But this does not indicate the dosing interval of sustained release oxymorphone.

The same is true of the other prior art references, which show dissolution, and in some instances sustained analgesia, for molecules other than oxymorphone. *See* Oshlack Reference at 14–25 (chlorpheniramine, morphine, oxycodone, hydromorphone, dilaudid, tramadol, and stearyl alcohol); Baichwal Reference Figs. 1–3 (showing both dissolution and pharmacokinetic profiles over twelve hours for the albuterol); '912 Patent Figs. 1–5 (showing analgesic effect and blood plasma concentrations over twelve hours of oxycodone); Webster Reference at 3 (morphine sulfate). The Cleary Reference, published in 2000, indicated that oxymorphone is "currently under development in sustained-release formulation[]" but gives absolutely no indication of dosing interval or twelve-hour efficacy. *See* Cleary Reference at 126.

In short, none of the prior art asserted would give any indication to a person of ordinary skill that *oxymorphone*, as opposed to some other substance, could be developed into a controlled-release formulation providing effective analgesia over a twelve-hour period.

Nor did any of the prior art references disclose the claimed food effects. In fact, defendants made no attempt at trial to show some teaching in the prior art of the food effects of controlled-release oxymorphone. Instead, they merely asserted that those effects were natural processes. And while immediate release oxymorphone's significant food effect is now known, it does not appear to have been known before 2001. *See, e.g.*, Physician's Desk Reference, Twenty-Third Edition (1969) at 698 (DTX-2890) (failing to indicate whether immediate release oxymorphone should be taken under fed or fasted conditions). Furthermore, there was no disclosure in the art that developing oxymorphone into a controlled release formulation would actually improve on immediate release oxymorphone's food effect as measured by AUC, *see supra* Part B(1)(a)(iii)(1), or predict the difference in AUC and C_{max} values claimed for fed and fasted conditions. *See, e.g.*, '122 Patent cl. 20.

The prior art also failed to teach the multiple peaks in blood concentration levels exhibited by controlled-release oxymorphone. At trial, Dr. Banakar testified that the prior art showed multiple-peaking for controlled release morphine and hydromorphone. *See* Trial Tr. at 1576–77. An article published in 1980 shows multiple peaks in controlled release morphine over a twelve hour period. *See* Leslie *et al.*, *Controlled Release Morphine Sulfate Tablets-A Study in Normal Volunteers*, 9 Br. J. Clin. Pharmac. 531, 534 (1980) (DTX-2816). Likewise, a patent issued in 1991 shows peaks in blood concentration levels of controlled release hydromorphone over twenty-four hours. *See* United States Paten 4,990,341 (the "Goldie Reference") at 8:20–30. But these sources did not

indicate whether *oxymorphone*, when housed in a controlled release setting, would exhibit multiple peaks.

The fact that two controlled-release opioids exhibit multiple peaks does not indicate that a wholly different controlled-release opioid will also exhibit multiple peaks. A defense expert, Dr. Mayersohn, baldly testified that "it is well established for a lot of opioids that you see multiple peaks," Trial Tr. at 1740:19–20, but he gave no indication of which of the nearly 70 opioids were known to do so in 2001. Unless a significant portion of all opioids were known to exhibit multiple peaks when developed into a controlled release formulation—something defendants did not come close to establishing at trial—there would be no reason for a person of ordinary skill in the art to think that oxymorphone would exhibit multiple peaks when developed into a controlled-release formulation. And while Endo certainly knew that oxymorphone in immediate release formulation exhibited dual peaks, *see* '216 Patent at Fig. 5, such information was not shown to be available to the public. Defendants simply failed to show how the known multiple-peaking of two controlled release opioids indicated multiple peaking for controlled-release oxymorphone.

Finally, defendants did not provide prior art disclosing the metabolite limitations of the Endo patents. At trial, defendants were quick to note that it was known that oxymorphone, when metabolized by the liver, produced detectable levels of 6-OH oxymorphone. *See* Trial Tr. at 1591. But where Endo claimed as a limitation "detectable blood plasma levels of 6-OH-oxymorphone and oxymorphone," it did so only in the conjunctive sense along with four other

limitations for the metabolite. *See* '216 Patent cl 1(i)-(v). Thus, while it was known that oxymorphone when metabolized produced 6-OH oxymorphone, *see* Cone *et al.*, *Oxymorphone Metabolism and Urinary Excretion in Human, Rat, Guinea Pig, Rabbit, and Dog*, 11 Drug Metabolism and Disposition 446, 446 (DTX-3554), the prior art taught neither the ratio of oxymorphone to its metabolite, nor the timing of peak metabolite levels, as required by the asserted claims. *See* '216 Patent cl. 1 (ii)-(iii).

3. Defendants' Convolution Analysis is Irrelevant Because it Relied on Data Not Found in the Prior Art.

In an effort to show the obviousness of the pharmacokinetic effects claimed in the '122 and '216 patents, defendants called a professor of pharmaceutical sciences, Dr. Michael Mayersohn, to testify that a person of ordinary skill in the art in 2001 could use a technique known as "convolution analysis" to predict the pharmacokinetic properties of controlled-release oxymorphone. Trial Tr. at 1706, 1713. The convolution analysis is a three-step process involving: (1) taking the "known" pharmacokinetic properties of immediate release oxymorphone; (2) taking the dissolution profile of known extended release opioids such as morphine; and (3) using computer modeling to combine the first and second steps and predict the pharmacokinetic properties of controlled-release oxymorphone. *See* Trial Tr. at 1721–23.

Dr. Mayersohn's convolution analysis was flawed from the outset because in 2001 there was no publicly available source disclosing the pharmacokinetic properties of immediate release oxymorphone. At trial, Endo's former chief

scientific officer, Dr. David Lee, testified that when Endo began developing oxymorphone into a controlled release formulation, there was a lack of published research on immediate release oxymorphone's pharmacokinetic properties. *See* Trial Tr. at 202. Although the FDA had approved oxymorphone for sale as the branded drug Numorphan in 1959, it did not at that time require efficacy data. *Id.* at 203:2. In fact, in 2001 there had been only four published studies on oral oxymorphone. *See* Briefing Packet (PTX-0223 at 410). Endo's project development team realized that oxymorphone was for all intents and purposes a "pharmacologic enigma." Trial Tr. at 203:11.

It was Endo's own development team that, beginning in 1998, performed the studies needed to measure immediate-release oxymorphone's pharmacokinetic effects. *See, e.g.*, EN3202 Project Team Minutes (6/26/98) (PTX-173 at 342627) (discussing the results of an eight-subject pilot pharmacokinetic study). It was only after Endo had studied the pharmacokinetic properties of immediate release oxymorphone that it could take the next step, and begin developing controlled release oxymorphone. *See* Trial Tr. at 197–99.

All of Endo's studies on immediate-release oxymorphone's pharmacokinetic effects were confidential, and as defendants' own expert testified, "not available in the literature." Trial Tr. at 1741:10–11; *see also* Excerpt from Endo Study EN3203-001 (DTX-1069A). But when Dr. Mayersohn performed his convolution analysis, he used Endo's information as a starting point. *See* Trial Tr. at 1758:1-4 ("Q. The study . . . which you relied on for oxymorphone pharmacokinetic profile data is an Endo study, right? A. Yes, sir.").

His only alternative would have been to conduct his own pharmacokinetic study, which he suggested could have been done by enlisting "six to perhaps ten human subjects." Trial Tr. 1741:18–19.

The court finds Dr. Mayersohn's testimony to be unpersuasive. Regardless of whether convolution analysis can be used to predict the pharmacokinetic effects of a new controlled release drug, it requires as its starting point pharmacokinetic data for the immediate release formulation. In performing his convolution analysis, Dr. Mayersohn used Endo's own pharmacokinetic data, information that would be unavailable to the public in 2001, and which simply does not constitute "prior art." Dr. Mayersohn's suggestion that an ordinarily skilled artisan could perform his own study to obtain such data misses the point. The fact is that there was no published source in 2001 disclosing the relevant pharmacokinetic properties of immediate release oxymorphone. Therefore, a person of ordinary skill in the art would have lacked the information necessary to perform a convolution analysis predicting the pharmacokinetic properties of controlled-release oxymorphone.

iv. Whether Secondary Considerations Indicate the Non-Obviousness of the Invention.

The final factor in the obviousness inquiry asks the court to consider objective indicia of non-obviousness, including the commercial success of the invention, the invention's satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

Endo was persuasive in demonstrating the commercial success of its

OPANA®ER products, and in relating the success of those products to the claims of the '122 and '216 patents. Endo's expert on commercial success, economist Dr. Gregory Bell, demonstrated that once OPANA®ER launched in 2006, it gained wide acceptance among physicians, going from zero prescriptions before launch to 350,000 prescriptions in 2011. Trial Tr. at 1994:1–2. During the same period, gross sales of OPANA®ER increased by a corresponding amount, from zero dollars in 2006 to well over $150 million in 2011. *See* PTX-0336 (showing IMS sales data by month). OPANA®ER achieved this growth despite facing competition from other long-acting opioids, including branded and generic morphine, methadone, and oxycodone. Trial Tr. at 1990–91. Since its launch in 2012, OPANA®ER CRF has experienced consistent sales, despite the entry of Actavis's generic tablets on the market. *Id.* at 1995.

In cross-examining Dr. Bell, defendants attempted to establish that OPANA's commercial success was more the result of aggressive advertising and rebate programs than the drug's inherent properties. Trial Tr. at 2046–48. But Dr. Bell demonstrated, to the court's satisfaction, a clear nexus between the asserted claims of the '122 and '216 patents and the market success of the branded product. As discussed at length in the preceding sections of this decision, key features of the invention include its twelve-hour dosing interval and analgesic effectiveness over the same period. When physicians were asked why they were prescribing OPANA®ER, they overwhelmingly attributed their decision to clinical properties such as the drug's ability to provide "effective pain relief," "good side effect profile" and "long duration of action." *See* Trial Tr. at

2012–13, *see also* PX4010.15 (showing the results of a physician survey). Physicians also cited other reasons attributable to the invention, including better tolerability and greater pain relief. *See* PX4010.15. Thus, the court is satisfied that OPANA®ER has achieved commercial success, and that there is a nexus between that success and the asserted claims of the '122 and '216 patents.

The court is also persuaded that the invention satisfied a long-felt but unmet need in the marketplace. Endo's expert on long-felt need, Dr. Edgar Ross, testified that the medical community had long sought additional tools to effectively combat chronic pain. *See* Trial Tr. at 935–37. At the time of the invention, there were numerous immediate release opioids on the market, but these had a short duration and often involved inconvenient routes of administration, such as intravenous and transdermal delivery. Trial Tr. at 941–42. Three controlled release opioids, morphine, methadone, and oxycodone, were on the market, but exhibited negative effect in some patients, including causing nausea and vomiting, poor interaction with other drugs, and diminished analgesic potency in patients unable to produce certain enzymes. Trial Tr. at 949–50. Overuse of the existing opioids could also result in increased tolerance, requiring physicians to either increase the dose, risking toxicity, or alternatively switch patients to a different opioid (opioid rotation). Trial Tr. at 952. The introduction of a new controlled-release opioid, oxymorphone, fulfilled the need for a drug with less side effects than those currently on the market, and the need for an additional option for use in opioid rotation. *Id.* at 952–53.

Others had failed to develop oxymorphone into a controlled release setting

before Endo, but have since copied that work. Endo developed OPANA®ER between 1997 and 2001, and launched it in 2006. Trial Tr. at 794:18–21. It was undisputed at trial that no entity had developed oxymorphone in an extended release formulation before then. It was only after OPANA®ER had demonstrated years of significant growth in sales and prescriptions that other companies decided to develop their own sustained-release oxymorphone products. *See* Trial Tr. at 1994:1–2. Indeed, the instant litigation involves attempts by generic drug manufacturers to do exactly that.

OPANA®ER experienced significant commercial success in the years following its launch despite the existence of branded and generic opioid competition. There was a clear need for an additional opioid for use in opioid rotation, as well as one that would be better tolerated by patients ill-disposed to morphine, methadone, and oxycodone. Finally, it is undisputed that no other entity had developed controlled-release oxymorphone before Endo, and that others only did so years after the drug's commercial success had been established. These secondary considerations indicate that the invention was non-obvious.

b. Whether the On-Sale Bar Applies.

Defendants argue that the '122 and '216 patents are invalid because the invention was ready for patenting and the subject of a commercial offer for sale more than a year before the patent applications were filed on October 15, 2001.

At trial, defendants' expert on the on-sale bar, Dr. Anthony Palmieri, testified that all of the dissolution and pharmacokinetic studies necessary to

achieve the claimed invention were performed before August of 2000. *See* Trial Tr. at 2307. Dr. Palmieri showed that for one dosage strength (20mg), OPANA®ER's formulation was determined as early as July of 1998. Trial Tr. at 2283. Moreover, Endo had completed a study on the *in vitro* dissolution rate of the tablets by October of that year. *See* EN3202 Formulation Development Report Part A EN3202 (PTX-0149 at 0634). Studies showing the dissolution and pharmacokinetic characteristics of the drug were performed by March of 2000. *See, e.g.*, Trial Tr. at 2290:16–18.

Finally, Dr. Palmieri testified that Endo knew the twelve-hour analgesic effect of its product by August of 2000. Trial Tr. at 2307. To support this assertion, Dr. Palmieri pointed to minutes from an August meeting between Endo and Penwest discussing the "preliminary results" from a study, study fifteen, showing that "EN3202 [OPANA] is an effective analgesic." *See* EN3202 Alliance Committee Meeting Minutes (Aug. 21, 2000) (PTX-589 at7886–87) (emphasis in original). These "preliminary results" were again discussed at a meeting of Endo's Project Team in September of 2000. *See* EN2302 Project Team Meeting Minutes at 1 (Sept. 14, 2000) (PTX-345) ("preliminary results are positive. . . EN3202 is an effective analgesic.").

Endo's expert, Dr. Edgar Ross, disputed the notion that the invention was ready for patenting before October 15, 2000. He explained that even though many of the studies on OPANA®ER (project name EN3202) had been completed before then, only the preliminary reports were available for some of them. Trial Tr. at 2816. Dr. Ross explained that preliminary reports cannot be completely

trusted until the data from the study is carefully scrutinized and memorialized in a final report. Trial Tr. at 2816. In the interim, results may change significantly if errors are discovered. *Id.*

The final report for study fifteen, which defendants suggested was completed in August of 2000, was not in fact issued until June 19, 2001. *See generally* Final Clinical Study Report, Double-Blind, Placebo Controlled . . . Comparison of the Efficacy and Safety of Controlled Release Oxymorphone . . . . (PTX-271). A final report for a study measuring controlled oxymorphone's "steady state" blood concentration levels was not issued until August 14, 2001. *See* A Randomized, Two-Period Crossover Trial Comparing the Single-Dose and Multiple-Dose (Steady State) Pharmacokinetics and Bioavailability of Numorphan CR and Numorphan IR Tablets Phase I (PTX-281).

The evidence does not demonstrate that the invention was ready for patenting more than a year before the applications were filed. As discussed in the claim construction section of this decision, a primary feature of the invention is that the dosage form will be "analgesically effective" for twelve hours, meaning it provides pain relief for that period. *See supra* Part A(1)(a). The invention could not be reduced to practice until the inventors were certain that it would provide the claimed analgesic effect. While preliminary reports indicated OPANA®ER's analgesic effectiveness, those results were not sufficiently trustworthy until the study data had been fully scrutinized. In the end, a mere two months separated the finalization of study nine, and just four months separated the finalization of study fifteen, from the filing of the '122 and '216 patent applications. Thus, the

court concludes that the invention was not ready for patenting before the "critical date."

Furthermore, the invention was not the subject of a commercial offer for sale before October 15, 2000. In June of 2000, Endo entered into a "Development and Clinical Supply Agreement" with drug manufacturer Novartis Consumer Health Inc. *See* Development and Clinical Supply Agreement at 1 (June 1, 2000) (PTX-347). The stated purpose of this agreement was for Novartis to manufacture tablets for Endo [redacted] *Id.* This was not a commercial offer for sale. To the extent a supply agreement could even be considered a "sale," the transaction was clearly experimental in nature, not commercial. *Id.* Because an NDA filing requires demonstrating to the FDA a drug's safety and efficacy, the "sale" of tablets for [redacted] will involve human and laboratory testing, clearly an experimental purpose. Indeed, the agreement explicitly assumes that [redacted] Since the Development and Supply Agreement involved a sale for [redacted], the court concludes that it was experimental in nature.

Because the invention was not ready for patenting nor the subject of a commercial offer for sale before October 15, 2000, the on-sale bar does not apply.

c. Whether the '122 and '216 Patents Satisfy the Requirements of 35 U.S.C. § 112.

Defendants argue that the '122 and '216 Patents fail to satisfy the definiteness, enablement, and written description requirements of 35 U.S.C.

§ 112(a).

With regard to definiteness, the court concludes that the claims give adequate notice of the metes and bounds of the invention. As discussed, there was some debate at trial over the definition of "peaks" at trial. The court viewed this debate as one primarily of construction, but it could be argued that the Endo patents' call for multiple "peaks," and to a lesser extent "detectable blood plasma levels," *see, e.g.*, '216 Patent at 26:35–55, would leave a skilled artisan in some doubt as to how those limitations could be satisfied. But as discussed, the definition of the term "peak" would be readily apparent to a person of ordinary skill in the art upon reading the specification. *See supra* Part A(1)(b). Moreover, the specification provides that the studies described in the patents were performed using "standard FDA procedures such as those employed in producing results for use in a new drug application." '216 Patent at 3:63–65. From this, an ordinarily skilled artisan would have known how to detect blood plasma levels of oxymorphone.

With regard to written description and enablement, the court concludes that the patents would reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date, and that such artisans would be able to make and use the invention without undue experimentation. Each of the features recited in the patent claims, such as an "oral controlled release oxymorphone formulation" of "about 5mg to about 80mg of oxymorphone" finds adequate, even abundant, support in the specification. *Compare* '216 Patent cl. 1 with '216 Patent at 4:37–40. Moreover, the patent

specifications are replete with examples of dosage forms satisfying each of the claimed limitations. *See, e.g.*, '216 Patent at 13–14. For example, the specification describes the administration to subjects of tablets containing 20mg of controlled-release oxymorphone, '216 Patent at 13:59–61, which were then shown to produce dissolution and pharmacokinetic characteristics within the ranges claimed. *Id.* at 14:59–15:20. The specifications also give detailed descriptions of the *in vitro* and *in vivo* testing methods employed in developing the tablets. *Id.* at 3–4. A person of ordinary skill in the art, upon reading the specifications, would be convinced that Endo possessed the invention claimed, and could also use the specification to develop his own tablets constituting the invention.

At trial, defendants' expert on indefiniteness, Dr. Arthur Kibbe, testified that certain of the asserted dissolution claims are overbroad. Trial Tr. at 1884–85. To wit, the specification shows the *in vitro* dissolution rate of three different formulations of OPANA®ER. *See* '122 Patent Table 4. The slowest-dissolving tablet had dissolved 27.8% after the first hour, and the fastest-dissolving tablet had dissolved 32.3% after the first hour. *Id.* However, when Endo wrote its dissolution claims, it recited a broader dissolution range of 15%–50% at one hour. *See, e.g.*, '122 Patent cl. 19. It recited similarly broad ranges at the four and ten hour marks. *See* Trial Tr. at 1891:5–13. In Dr. Kibbe's view, these broad ranges indicate that the claims are insufficiently described in the specification. *See* Trial Tr. at 1879.

Defendants have not persuasively shown that the dissolution claims are

so broad as to fail to inform an artisan that Endo possessed the invention claimed. A person of ordinary skill in the art, upon reading the dissolution ranges, would understand that the inventors had chosen ranges encompassing the invention, and also allowing for variations. Indeed, had the claims been more restrictively drawn they would have invited infringement. If, for example, Endo had claimed a dissolution range at the first hour of 27%–33%, generic manufacturers could escape infringement by formulating a tablet that dissolves at 26% percent at one hour, or that dissolves at 34% at one hour. The ordinarily skilled artisan, upon reading broader claims, would understand them to encompass the invention as claimed and possessed by the inventor.

The court concludes that the asserted claims, including the dissolution claims, would convey to those skilled in the art the metes and bounds of the invention and that Endo possessed the invention as claimed. Moreover an artisan, upon reading the claims and specifications, would be able to formulate his own controlled-release oxymorphone tablets. Thus, the '122 and '216 patents satisfy the written description, enablement, and definiteness requirements of 35 U.S.C. § 112.

Conclusion Regarding the Validity of the '122 and '216 Patents

Defendants have failed to show, by clear and convincing evidence, that the '122 and '216 patents are invalid. Defendants did not assert that the patents are anticipated. With regard to obviousness, the art revealed no motivation to select oxymorphone for use in a controlled-release formulation, and it failed to disclose the matters recited in the asserted claims. Even if an artisan were somehow

motivated to select oxymorphone for use in a controlled release setting, he would have no reasonable expectation of success in doing so given the failure of the art to disclose the pharmacokinetic and dissolution characteristics. Moreover, secondary considerations strongly indicate the invention's non-obviousness. Because defendants' other defenses are without merit, the court concludes that they have failed to carry their burden and have not shown, by clear and convincing evidence, that the '122 and '216 patents are invalid.

2. Whether the Asserted Claims of the '060 Patent are Invalid.

Defendants also challenge the validity of the final patent-in-suit, the '060 Patent. Abuse-deterrence is the primary feature of the invention embodied in the '060 Patent, and is achieved through the tablet's exceptional hardness and its ability to accommodate secondary barriers. As discussed, Endo licensed the '060 Patent from co-plaintiff Grünenthal in order to develop OPANA®ER into a crush-resistant formulation. Endo and Grünenthal now assert infringement of the '060 Patent by those defendants seeking approval to market crush-resistant oxymorphone tablets. Crucial to the instant litigation, then, is whether defendants have carried their burden in showing the '060 Patent to be invalid.

The '060 Patent reflects research and development performed by Grünenthal and its former head of pharmaceutic development, Dr. Johannes Bartholomäus. Grünenthal began exploring abuse-deterrent technologies in response to the growth in the abuse of prescription opioids, including the widespread abuse of OxyContin in the United States. *See* Trial Tr. at 984. Early on, Dr. Bartholomäus tested a number of ideas for combatting tablet abuse,

including the use of antagonists which block the action of the opiate in the body. *See* Trial Tr. at 989:22–24; 993:3–5. However, Grünenthal found each of these solutions to be inadequate.

In November of 2002, Dr. Bartholomäus gave a presentation suggesting the company explore other ways to combat abuse, such as making the tablets harder. *See* Trial Tr. at 999–1000. He suggested using PEO to "increase [the] mechanical resistance of tablets." Presentation at 19 (Nov. 11, 2002) (PTX-2199). After the presentation, Dr. Bartholomäus put this idea to work in the laboratory, making tablets solely out of compressed PEO. Trial Tr. at 1006. Those tablets proved to be exceptionally strong and resistant to crushing. Trial Tr. at 1007. However, the strength of the tablets evaporated when Dr. Bartholomäus added an opiate to them. *Id.* Adding the opiate seemed to "destroy" the hardness conferred by the PEO. *Id.*

Dr. Bartholomäus went on to conduct further experiments on mixtures of PEO and opiates. Eventually, he realized that by heating the mixture and forming it using a die and punches, he could create an opioid/PEO tablet of exceptional hardness. Trial Tr. at 1008–10. Not only was the tablet exceptionally hard, able to withstand 500N of pressure, it also dissolved in conditions mimicking the human body, releasing the opioid. Trial Tr. at 1011:11–15. Upon showing this to his managers, Dr. Bartholomäus set out to develop a process to mass produce the tablets. Trial Tr. at 1015:21–22. Over the next year, he and another inventor, Dr. Elisabeth Arkenau, did just that. Trial Tr. at 1016:14–16. Their work ultimately resulted in the '060 Patent.

Defendants argue that the '060 Patent is invalid for three reasons: (a) previous decisions of this court have a collateral effect establishing the invalidity of the asserted claims; (b) a prior art reference known as the McGinity Application anticipates the asserted claims; and (c) the asserted claims would have been obvious to a person of ordinary skill in the art at the time of the invention. The court will address each of these arguments in turn.

a. The Collateral Effect of This Court's Prior Decisions.

Defendants argue that a prior case in this court preclusively establishes that a piece of prior art known as the McGinity Application anticipates the asserted claims of the '060 Patent.

The "McGinity Application" is a patent application filed in 1997 by James McGinity and others to the World Intellectual Property Organization. *See* International Patent Application Publication WO 97/49384 (DTX-0098 at 2408) (the "McGinity Application"). The McGinity Application teaches the creation of controlled-release drugs using hot-melt extrusion. *Id.* at 11. Hot melt extrusion occurs in three steps consisting of combining a powdered-therapeutic compound with PEO and other optional components; and placing the mixture in an "extruder hopper" which is heated to a temperature that will melt or soften the PEO. The softened mixture then exits the extruder through a die; and still warm, is shaped, molded, chopped, cut, or tableted into the desired physical form. *Id.* at 11:28–30.

In addition to asserting the '060 Patent in this litigation, Grünenthal had also initially asserted two other patents, United States patent numbers

8,114,383 (the "'383 Patent") and 8,192,722 (the "'722 Patent"). Grünenthal's assertion of the '383 Patent was significant because it had asserted that same patent in a different case before this court involving the prescription drug OxyContin. In 2014, following a month-long bench trial, Judge Stein issued a decision concluding that the asserted claims of the '383 Patent were invalid as anticipated by the McGinity Application. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 424 (S.D.N.Y. 2014).

In light of Judge Stein's decision, defendants in these actions filed a motion for partial summary judgment, arguing that the decision precluded Grünenthal from litigating the asserted claims of the '060, '383, and '722 patents here. *See* Dkt. No. 70, *Endo Pharmaceuticals Inc. et al v. Actavis Inc. et al.*, No. 13-CV-00436. The undersigned agreed in part, recognizing that Judge Stein had expressly invalidated (as anticipated by McGinity) four of the five asserted claims of the '383 Patent, and that his decision precluded litigation of those claims here. *See* Opinion of March 17, 2015 at 4 (Dkt. #117 in Case 13-cv-00436) (the "March 17th Opinion"). The court also recognized a collateral effect with regard to the final asserted claim of the '383 Patent. *See id.* at 5. However, the court held that there was no collateral effect with regard to the '060 Patent because that patent was never asserted before Judge Stein and, more importantly, recited limitations concerning abuse-deterrence absent from the adjudicated claims of the '383 Patent. *Id.* at 6–7.

Although the undersigned had rejected their collateral estoppel theory with regard to the '060 Patent, defendants continued to press the argument at trial,

arguing that the similarities between the '383 Patent and the '060 Patent are so pronounced as to require a preclusive effect. *See* Trial Tr. at 135–36. *See also* Side By Side Comparison (DX-9001).

The court finds no need to revise its holding regarding the OxyContin decision's lack of a preclusive effect on the asserted claims of the '060 Patent. As the undersigned noted in the March 17th Opinion, there are "intriguing similarities" between the '383 and '060 patents. However, the '060 Patent has a crucial difference: it describes an *abuse-proofed* dosage form. *See* '060 Patent Claim 1. All of the asserted claims of the '060 Patent share this limitation. *See* '060 Patent cls. 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34 (all depending from Claim 1 or from claims themselves depending therefrom). Moreover, Claim 9 of the '060 Patent recites six additional barriers to abuse. '060 Patent at 21:37–51. In contrast, the asserted claims of the '383 Patent made no mention of abuse-proofing, nor did they recite additional barriers to abuse. *See* '383 Patent at 21–22. Thus, Judge Stein made no findings or conclusions as to whether an "abuse-proofed" dosage form would be invalid in light of the prior art, either through anticipation or obviousness. Consequently, the undersigned will not revise the holding that Judge Stein's decision regarding the '383 Patent does not preclude litigation of the asserted claims of the '060 Patent here.

b. Whether the Asserted Claims Are Anticipated by the McGinity Application.

Defendants argue that the McGinity Application anticipates the asserted claims of the '060 Patent. A prior art reference anticipates—and invalidates—the asserted claims only if it expressly or inherently discloses each of the invention's

claimed elements. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The primary element of the asserted claims of the '060 Patent is that the tablets will be "abuse-proofed," *see* '060 Patent cl. 1, meaning they reduce the potential for abuse, by among other things exhibiting exceptional hardness. *See supra* Part (A)(1)(c)(i).

The McGinity Application is silent regarding abuse reduction. It describes the process of hot-melt extrusion, but does not say whether the process could produce abuse-proofed dosage forms or even dosage forms of unusual strength. Indeed, the words "abuse," "crush," "hardness," "breaking," "strength," "newtons," "snort," "inject," "insufflate," etc… are wholly absent from the McGinity Application. Thus, the McGinity Application, while teaching a process for creating controlled-release tablets using hot-melt extrusion, fails to expressly disclose abuse-proofing.

In order to show anticipation, then, it was incumbent on defendants to prove at trial that abuse-proofing is inherent to tablets made pursuant to the McGinity Application. To this end, Defendants' expert on invalidity, Dr. Fernando Muzzio, testified that any tablet made using the process described in the McGinity Application would be "abuse-proofed" because it would be exceptionally hard. *See* Trial Tr. at 2164–65. Dr. Muzzio tested this theory in the laboratory. He read the experiments disclosed in the McGinity Application and made tablets replicating those experiments. Trial Tr. at 2168. He then inserted his "McGinity tablets" into an Instron testing devise and determined their breaking strength. *Id.* None of the tested tablets broke when subjected to

pressures above 500N. *See* Excerpt of the Final Muzzio Report at 36, (DTX-5119A). Indeed, video presented at trial showed that the McGinity tablets remained entirely whole. Thus, Dr. Muzzio concluded that tablets made pursuant to the McGinity Application are inevitably hard, and thus inevitably resistant to abuse through crushing.

The court is not persuaded that the McGinity Application inherently discloses abuse-proofing. In order to have an "abuse-proofed tablet," the tablet must contain an ingredient that is known to have abuse potential, such as the oxymorphone in plaintiffs' tablets. Indeed, McGinity discloses that the invention can be used with analgesics. *See* McGinity Application at 8:20-35. Some analgesics, notably opioids, were known to have abuse potential. But in creating his tablets, Dr. Muzzio did not use an opioid or any other active ingredient with abuse potential. Rather, Dr. Muzzio created his McGinity tablets using the cancer drug chlorpheniramine maleate ("CPM"). Trial Tr. at 2496:3; *see also* Expert Report of Fernando J. Muzzio, Ph.D. Ex. B at 2 (DTX-5119A) ("All of the formulations to be tested in this work are composed of . . . Chlorpheniramine Maleate."). Chlorpheniramine maleate, as Dr. Muzzio conceded at trial, is not known to have abuse potential. Trial Tr. at 2200:22–23.

The court can only speculate as to why Dr. Muzzio, in attempting to show that the practice of the McGinity Application would inevitably result in abuse-proofed tablets, chose to use an active ingredient that is not prone to abuse. Perhaps he felt confined to the active ingredient actually used in McGinity's examples. *See* McGinity Application at 19 (using CPM). But as Dr.

Bartholomäus's early experiments with PEO showed, the introduction of a novel ingredient can dramatically alter PEO's hardness-conferring properties. Trial Tr. at 1006-07 ("I saw from this that mixing and adding this opiate . . . with this polyethylene oxide, this PEO, does destroy any properties that PEO might have to form a high crushing strength tablet."). This is confirmed by McGinity, which expressly teaches that "particular combinations of therapeutic compound and PEO (of given molecular weight) will result in various formulations each possessing its particular combination of properties." McGinity Application at 3:15–17.

If Dr. Muzzio wished to establish that McGinity tablets are inevitably abuse-proofed because of their hardness, he should have used an active ingredient known to have abuse potential, such as an analgesic. Because he did not do so, he merely succeeded in showing that hot-melt extrusion of PEO and chlorpheniramine maleate ("CPM") will result in hard, even astoundingly hard, tablets. *See* Muzzio Report at 35 (DTX-5119a) (showing breaking strengths between 2,000 and 4,500 newtons). But such tablets cannot be said to be abuse-proofed because they have no ingredient with abuse-potential.

Moreover, the McGinity application is silent with regard to the type of additional barriers to abuse contained in Claim 9 of the '060 Patent. *See* '060 Patent at 21:37–51. It does not disclose irritants, viscosity increasing agents, antagonists, emetics, dyes, or bitter substances as required by the claim.

Dr. Muzzio's tests clearly demonstrate that the process taught in the McGinity Application, the hot-melt-extrusion of PEO and a therapeutic

compound, will result in exceptionally hard tablets, and this demonstration is significant to the court's obviousness analysis. But given Dr. Muzzio's decision to use an active ingredient without abuse potential, the court feels that defendants fall slightly short of carrying their burden in showing anticipation.

Defendants have not persuasively shown that McGinity inherently discloses abuse-proofing, and neither have they shown that McGinity discloses the additional barriers to abuse recited in Claim 9. Thus, the court concludes that defendants have not carried their burden in showing that the McGinity Application anticipates the asserted claims of the '060 Patent.

c. Whether the Asserted Claims of the '060 Patent Would Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of the Invention.

The next step in determining whether the '060 Patent is invalid is to consider whether the asserted claims of the '060 Patent would have been obvious, in light of the prior art, to an ordinarily skilled artisan in 2003.[20] At trial, the parties identified three areas in dispute regarding the obviousness of the invention: (i) whether there was a motivation in the prior art to develop unusually hard tablets as a means of reducing the abuse of opioids; (ii) whether the prior art discloses the limitations of the asserted claims of the '060 Patent; and (iii) whether secondary considerations indicate the invention's non-obviousness.

i. Whether There Was a Motivation to Make Unusually Hard Tablets as a Means of Reducing Opioid Abuse.

[20] As a divisional application of the '383 Patent, the '060 Patent is entitled to that patent's filing date for obviousness purposes. *See* 35 U.S.C. § 120.

Defendants argue that there was a motivation in the art to make unusually hard tablets as a means of reducing opioid abuse. *See* Trial Tr. at 2187–88. Defendants rely on three patents to support this assertion: United States Patent Number 7,968,119 (the "'119 Patent"); United States Patent Number 6,696,088 (the "'088 Patent"); and United States Patent Number 7,33,182 (the "'182 Patent"). The applications for each of these patents were filed before 2003. Defendants also rely on a body of art from 2002 related to the branded stimulant Concerta.

The '119 Patent shows knowledge in the art of the abuse of narcotics, including opioids and oxymorphone, through crushing and other means. It describes the invention of a "tamper proof system for delivery of narcotics." *See* '119 Patent at 1: 15-18 (DTX-161). It describes combining an active ingredient with an antagonist. *Id.* at 3–4. When the drug is taken properly, the active ingredient will provide the desired effect long before the antagonist is activated. *Id.* at 4:1–9. However, when the dosage form is tampered with, through "adulteration, distillation, or *pulverization*," the antagonist will be activated and block the euphoric effect of the drug. *Id.* at 4:50–64 (emphasis added). At the same time, tampering will "induc[e] a bowel movement in the subject" resulting in "rapid detoxification." *Id.* at 3–4.

The '088 and '182 patents also show knowledge in the art of opioid abuse through crushing. The '088 Patent, like the '119 Patent, uses an antagonist that only activates once the dosage form is "tampered with" by "crushing" or

"shearing." '088 Patent at 7:38–40. Similarly, the '182 Patent suggests using an antagonist, as well as aversive agents (an irritant), to reduce tampering of the dosage form through crushing, shearing, grinding, and dissolving. *See* '182 Patent at 4:55–59.

These pieces of art show that there was knowledge of opioid abuse through crushing, and thus show some motivation to solve that problem. However, they do not show a motivation to select hardness as the solution. To the contrary, the '119, '088, and '182 patents taught away from selecting hardness as an abuse-deterrent feature because their antagonists are released when the dosage form is pulverized, sheared, crushed or ground. *See, e.g.*, 119 Patent at 3–4. To a person of ordinary skill in the art, patents teaching the use of crush-activated antagonists to deter abuse would not also teach crush-resistance (hardness) as a feature to deter abuse.

Defendants are more persuasive in arguing that the prior art surrounding the branded drug Concerta taught the use of exceptional hardness to deter drug abuse. Trial Tr. at 2189. Concerta is a branded stimulant used in the treatment of Attention-Deficit/Hyperactivity Disorder. *See* Letter to the Editor of the Journal of the American Academy of Child & Adolescent Psychiatry (2002) (DTX-84 at 0759). It uses a technology, OROS, to deter abuse. An OROS tablet is designed to act as an "osmotic pump." Trial Tr. at 2517:8–9. The outside layer of the tablet consists of a semi-permeable membrane that absorbs water, allowing the inside contents of the tablet (containing the active ingredient and PEO) to be dissolved and slowly pushed out through a hole at the top of the tablet. Trial Tr.

at 2522.

Four pieces of prior art in 2002 indicated that Concerta was known to be hard, and also known to deter abuse through crushing. A magazine article stated that Concerta is "difficult to abuse because . . . in [its] time-release form, [it] can't be chopped and snorted." Craig Donnelly, MD., ADHD Medications Past and Future, 22 *Behavioral Health Management* 28, 29 (2002) (DTX-2554). An article in the Sacramento Bee newspaper stated that Concerta's manufacturer, McNeil, had "released a fact sheet stating that Concerta is hard to abuse because it is difficult to crush." Dorsey Griffith, *Potential New ADHD Drug Creating Lots of Big Hopes*, Sacramento Bee (Oct. 30, 2002) (DTX-82 at 0754). An article in Child & Adolescent Psychiatry indicated that Concerta is "resistant to diversion (cannot be ground up or snorted), [and] is well suited for treatment of adolescents. Greenhill *et al.*, *Practice Parameter for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults*, 41 J. Am. Acad. Child Adolescent Psychiatry (Feb. 2002) (DTX-80 at 0745). Finally, a letter to the editor in the same journal indicated that the ingredient in the "Concerta tablet is very difficult . . . to crush if the tablet is chewed accidentally." Ciccone, P. E., *Attempted Abuse of Concerta*, Letters to the Editor, J. Am. Acad. Child Adolescent Psychiatry, 41:7 (July 2002) (DTX-100). This significant body of art shows knowledge of hardness as a feature to deter abuse through crushing.

Plaintiffs' experts dispute Concerta's teaching. Dr. Bartholomäus testified that he knew of the OROS technology (the tablet technology used in Concerta) in 2002, but didn't believe OROS tablets to be crush-resistant because his team

"bought some OROS from the U.S. market, took it to Germany, worked on it, and we could crush it. So it didn't solve the problem of crushing." Trial Tr. at 1000:21–23. Similarly, Dr. Davis testified that OROS was easily subverted by peeling off the outer membrane, "like the skin of an orange," and that once the outer membrane is removed the tablet becomes "quite soft." Trial Tr. at 2519: 11-13; 2520:4.

Plaintiffs have not persuasively countered defendants' assertion that the body of art surrounding Concerta would indicate hardness as a means of deterring abuse. The fact that Dr. Bartholomäus knew of OROS in 2002, and was motivated to test its hardness with a mortar and pestle, indicates that other ordinarily skilled artisans would also be motivated to explore exceptional hardness as an abuse-deterrent feature. Both his and Dr. Davis's observation that OROS is easily subverted by peeling is irrelevant as to whether a motivation to develop hard tablets was taught by the prior art.

The art surrounding antagonist-based tablets demonstrated a motivation to solve the problem of crushing prescription drugs. The Concerta art made the same observation, and also indicated the use of hardness as a solution. While Concerta's active ingredient was a stimulant, an ordinarily skilled artisan would readily understand it to teach the abuse-deterring value of hardness for other active ingredients, including opioids. Thus, the court is persuaded that there was a motivation in the art to solve the crushing of opioids by making tablets of exceptional hardness.

ii. Whether the Prior Art Discloses the Limitations of the Asserted Claims of the '060

Patent.

At trial, the parties disputed whether the prior art discloses: (1) an abuse-proofed thermoformed dosage form; comprising (2) one or more active ingredients with abuse potential and (3) at least one synthetic or natural polymer with a weight of at least 0.5 million according to rheological measurements; and more specifically the polymer polyethylene oxide; and (4) which exhibits a breaking strength of 500N; and (5) the six additional barriers to abuse recited in Claim 9 of the '060 Patent.

1. The Prior Art Discloses Thermoforming and Abuse Proofing.

The McGinity Application discloses thermoforming. As discussed in the claim construction section of this opinion, a thermoformed dosage form is one created by applying pressure to a mixture of an active ingredient and a high molecular weight polymer and exposing the mixture to the prior, simultaneous, or subsequent application of heat. *See supra* Part A(1)(c)(ii). The McGinity Application describes a dramatically similar process, hot melt extrusion, involving mixing a therapeutic compound with high molecular weight PEO, placing the mixture into an extruder which is heated, and then pushing that mixture through a die. *See* McGinity Application at 11:18–33. These two processes are so similar that at trial, experts for both sides referred to hot-melt extrusion as a type of thermoforming. *E.g.*, Trial Tr. at 1083:25–1084:2 ("Now hot melt extrusion is a type of thermoformed dosage form, yes? [BANAKAR] A. In general, yes . . . ."). Because hot-melt-extrusion shares the key features of thermoforming, the court concludes that the McGinity Application discloses a

"thermoformed dosage form" as required by the asserted claims.

Regarding "abuse-proofing," there is a substantial body of prior art showing that the use of PEO and hot melt extrusion will result in tablets of unusual hardness, thus reducing the potential for abuse by crushing. PEO's strengthening properties were certainly known. A patent awarded in 1992 provided that "it is preferred to increase the hardness of the excipient by adding a small amount of polyethylene oxide (PEO) having a molecular weight from about 100,000 to about 500,000 daltons. The high molecular weight polyethylene oxide contributes strength to the molded dosage form and reduces brittleness." *See* United States Patent 5,139,790 at 5:19–28 (DTX-75). Likewise, a journal article showed that compressed tablets containing PEO in various proportions exhibits a breaking strength up to 255N, s*ee* L. Maggi *et al.*, *Dissolution Behaviour of Hydrophilic Matrix Tablets Containing Two Different Polyethylene Oxides (Peos) For The Controlled Release Of A Water Soluble Drug*, 23 Biomaterials 23: 1113, 1119 (2002) (DTX-76), which is above the known breaking strength of regular tablets (100N-200N). *See* Trial Tr. at Trial Tr. at 1024:13–14; 2528:24.

Hot melt extrusion was also known to increase the strength of tablets. A dissertation published in 1999 by Feng Zhang, co-inventor on the McGinity Application, provided that "hot-melt extrudate is anticipated to possess a higher physical strength . . . than tablets prepared by . . . direct compression." Zhang, Feng, *Hot-Melt Extrusion as a Novel Technology to Prepare Sustained-Release Dosage Forms* at 69 (DTX-170). Similarly, an article co-authored by Zhang and

McGinity in 2001 provides that "When compared with traditional [melt granulation] HME [hot melt extrusion] produced harder tablets." Liu *et al.*, *Properties of Lipophilic Matrix Tablets Containing Phenylpropanolamine Hydrochloride Prepared by Hot-Melt Extrusion*, 52 European J. of Pharmaceutics and Biopharmaceutics 181, 190 (2001) (DTX-141). Indeed, four other pieces of prior art disclose hot-melt-extrusion's value in creating hard tablets. *See* (DTX-139), (DTX-137); (DTX-153); (DTX-164).

The court is persuaded that a person of ordinary skill in the art would understand that a thermoformed tablet containing PEO would be unusually hard. An unusually hard tablet is more difficult to crush than a softer tablet, and thus would reduce the potential for abuse by crushing. Thus, the prior art discloses "an abuse-proofed thermoformed dosage form as required by Claim 1 and the dependent claims of the '060 Patent.

2. The McGinity Application Discloses Active Ingredients With Abuse Potential.

The McGinity Application also discloses active ingredients with abuse potential, including opioids. The invention calls for the mixture of PEO and a "therapeutic compound." McGinity Application at 2:25–29. It defines "therapeutic compounds" to include a host of substances, including valium (diazepam). *Id.* at 8. As Dr. Davis conceded at trial, valium is known to be addictive. Trial Tr. at 2556:2–5.

McGinity also lists analgesics as suitable therapeutic compounds. McGinity Application at 8:20. In 2002, it was well understood that opioids are

analgesics. *See, e.g.*, Remington's Pharmaceutical Sciences 17 at 1103–05 (1985) (DTX-3201) (describing oxymorphone hydrochloride as one of several semisynthetic opiate analgesics); *see also* Goodman *et al.*, *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 491 (1985) (DTX-2781) ("The opioids are employed primarily as analgesics . . . ."). A person of ordinary skill in the art, upon reading McGinity's disclosure of analgesics, would understand that analgesics include the known opioids, including oxycodone and oxymorphone. Thus, the McGinity Application discloses active ingredients with abuse potential, such as valium and opioids such as oxycodone and oxymorphone. Consequently, the McGinity Application discloses the relevant portions of Claim 1 of the '060 Patent ("one or more active ingredients with abuse potential"), and the relevant portions of claims 31 and 34 of the '060 Patent, which specify oxycodone and oxymorphone. *See* '060 Patent at 24:3–5; 13–15.

3. The McGinity Application Discloses the Polymer Limitations of the Asserted Claims.

The McGinity Application also discloses the various limitations of the asserted claims relating to the polymer used. McGinity discussed the use of high-molecular weight (1,000,000 – 10,000,000) PEO for use in hot melt extrusion, and actually tested numerous examples of tablets using such high-molecular weight PEO. *See* McGinity Application at 5:3–4; 19:11–34 (listing molecular weights of 1 million and 7 million). Thus, McGinity discloses the relevant limitations of claims 1, 4, and 30 of the '060 Patent, which require: (1) "at least one synthetic or natural polymer with a weight of at least 0.5 million;" that (4)

the polymer be selected from the "group consisting of polyethylene oxide;" and (30) that "the . . . polyethylene oxide have a molecular weight of from 1–15 million." *See* '060 Patent at 21:7–10, 19–24; 23:19–20. Because most of the McGinity's tablets used PEO in proportions greater than 60% by weight, *see* McGinity Application at 19:15–33 (listing percentages of weight between 54% and 94%), it also discloses the substance of Claim 33 of the '060 Patent. *See* '060 Patent at 24:7–10 ("wherein the content of the polymer is at least 30% [corrected to 60%] by weight relative to the total weight of the dosage form."). Finally, because McGinity provided that "the therapeutic compound may be . . . suspended in the polymer matrix of the formulation," *see* McGinity Application at 8:6–7, it discloses the substance of Claim 24 of the '060 Patent, which provides that the polymer "also serve[s] as a controlled release matrix material." *See* '060 Patent at 22:65–7.

4. The McGinity Application Discloses Breaking Strength in Excess of 500N.

While Dr. Muzzio's recreation of the McGinity Application failed to inherently disclose abuse-proofing in the anticipation context (because he failed to use an ingredient with abuse potential), *see supra* Part B(2)(b), his tests succeeded in showing that McGinity inherently discloses breaking strengths above 500N. Indeed, Dr. Muzzio created hundreds of tablets according to the McGinity Application's examples, and each of these tablets exhibited a breaking strength well above 2000N. *See* Muzzio Report at 34–36 (DTX-5119A). At trial, plaintiffs raised various criticisms of Dr. Muzzio's methods, *see, e.g.*, Trial Tr. at

2219 (noting that Dr. Muzzio had failed to record torque values), but the court finds these criticisms to be outweighed by the sheer breadth and thoroughness of his testing. Thus, the court is persuaded that the McGinity Application inherently discloses breaking strengths in excess of 500N as required Claim 1 of the '060 Patent. *See* '060 Patent at 21:12–13.

5. The Prior Art Discloses the Additional Barriers to Abuse Recited in Claim 9 of the '060 Patent.

Claim 9 of the '060 Patent recites six additional barriers to abuse to be incorporated into the dosage form. *See* '060 Patent at 21:37–51. These are: an irritant, a viscosity-increasing agent which forms a gel with the extract from the dosage form, an antagonist, an emetic (vomiting agent), a dye, and a bitter substance. *See* '060 Patent at 21:38–51. Each of these additional barriers to abuse is disclosed in the prior art.

Irritants were disclosed in a number of references, including a patent application filed in 2002 which described creating a dosage form incorporating an antagonist and "an irritant in an effective amount to impart an irritating sensation to an abuser upon administration of the dosage form after tampering." *See* Abstract, United States Patent No. 7,332,182 (DTX-160). The reference expressly discloses the irritant capsaicin, the active ingredient in peppers. *Id.* at 6:59. The specification of the '060 Patent discusses the use of peppers and other "capsaicinoids" as irritants. *See* '060 Patent at 8:10. Thus, the court concludes that the prior art discloses the use of irritants described in Claim 9 part (a) of the '060 Patent.

The prior art also discloses the use of viscosity increasing agents. As discussed in the claim construction section of this opinion, a "viscosity increasing agent" is a substance, distinct from the hardening polymer, which increases the thickness of the dosage form extract by forming a gel when exposed to a liquid, such gel optionally remaining visually distinguishable. *See supra* Part(A)(1)(c)(iv). At trial, Dr. Muzzio explained that the McGinity Application discloses several substances that are known to be viscosity increasing agents, such as guar gum and alginic acid. Trial. Tr. at 2178:14–18; *see also* McGinity Application 13:27–30 (listing guar gum and alginic acid as "disintegrating agents"). This is important because Guar gum was later listed in the '060 Patent as being a viscosity-increasing agent. '060 Patent at 9:7. Thus, McGinity discloses distinct viscosity-increasing agents as required by Claim 9.

Antagonists, emetics, dyes, and bitter substances were well known in the art. The '119, '088, and '182 patent applications, each filed before 2003, all describe the use of antagonists to deter abuse of prescription drugs. *See supra* Part (B)(2)(c)(i). Emetics, like the syrup of ipecac, were commercially available, as were dyes and bitter substances. *See* Trial Tr. at 1105-06.

The court is persuaded that each of the additional barriers to abuse recited in Claim 9 of the '060 Patent were disclosed in the prior art. Moreover, once an artisan had set out to create an abuse-proofed tablet, it would have been obvious to integrate one or more of these additional barriers along with the feature of unusual hardness as required by the claim. *See* '060 Patent at 21:37. Indeed, much of the prior art used a multiple-barrier approach, integrating two or more

features, such as the use of an antagonist and irritant, to prevent abuse. *See, e.g.*, '182 Patent at 2:67–33 (DTX-161

Thus, the court concludes that the prior art discloses the substance of Claim 9 of the '060 Patent. Likewise, claims 25, 26, and 27, which also incorporate additional barriers to abuse, were also disclosed. To the extent those claims recite "press-forming" and a "melt process" as additional limitation, those limitations were disclosed by the McGinity Application, which teaches "compression molding" and hot-melt extrusion. *See* McGinity Application at 11:-8.

The court concludes that each limitation of the asserted claims of the '060 Patent was disclosed in the prior art. The McGinity Application, while insufficient to anticipate the invention, nonetheless discloses many of its components. The remainder of the components were disclosed by other references.

iii. Whether Secondary Considerations Indicate the Non-Obviousness of the '060 Patent.

The final step in the obviousness analysis requires consideration of objective indicia of non-obviousness, such as the commercial success of the invention, the invention's satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

The commercial success of the invention indicates its non-obviousness. At trial, Dr. Alexander Kraus, explained that Grünenthal has successfully licensed its crush-resistance technology to branded-drug manufactures Johnson & Johnson, Purdue Pharma, and Endo, for use in their flagship opioid products.

Trial Tr. at 1380. The revenue from these licenses is significant. Revenues earned from reaching certain development milestones with these companies total 116 million euros. *Id.* at 1391. In addition, these companies have paid Grünenthal royalties totaling 312 million euros. *Id.* In all, Grünenthal has earned 428 million euros, or $556 million, from licensing its crush-resistant technology to American branded-drug manufacturers. Trial Tr. at 1392:5–10. Thus, Grünenthal has enjoyed clear and indisputable commercial success for its product. This success is directly related to the asserted claims, because each of the license agreements involved developing abuse-deterrent dosage forms, and abuse-deterrence is the primary feature of the asserted claims of the '060 Patent. *See* Trial Tr. at 1385–88.

However, there does not appear to have been a long-felt need for the invention. Dr. Bartholomäus testified that Grünenthal began exploring abuse deterrence to confront the crisis of OxyContin abuse in the United States. Trial Tr. at 984:15–19. Dr. Lee testified that OxyContin only achieved widespread use "in the late '90's." Trial Tr. at 236:5–7. And it didn't become widely abused until the early 2000's. *See* Trial Tr. at 2840:10–24. Thus, there was at most only a few years separating the rise of OxyContin abuse and Grünenthal's invention.

Moreover, Grünenthal's evidence of skepticism and industry acclaim is unpersuasive. As evidence of skepticism, Grünenthal's experts testified that the company was met with incredulity when it first set out to sell its technology. *See, e.g.*, Trial Tr. at 2542–43 ("[W]hen he [Bartholomäus] first began describing his invention, people were skeptical. His colleagues at Grünenthal were skeptical,

people from Purdue or from Endo who were interested in the technology were skeptical . . . ."). Members of the industry doubted that a tablet as hard as Grünenthal's could actually release the active ingredient. *Id.* at 2543. Grünenthal offered similar "evidence" of industry acclaim. Trial Tr. at 2545. ("The potential licensees, when they visited Grünenthal and saw the technology and saw not just the hardness but the release data, were indeed impressed. And I think a couple of the people said this is the best technology we have seen so far to date."). In the court's view, this evidence is too anecdotal to be useful. Grünenthal failed to provide tangible evidence that its invention was met with anything more than passing incredulity, and its only evidence of industry acclaim is secondhand and underwhelming.

Conclusion Regarding the Validity of the '060 Patent

Defendants have shown, by clear and convincing evidence, that the asserted claims of the '060 Patent would have been obvious to a person of ordinary skill in the art at the time of the invention. The art in 2002 demonstrated a clear motivation to solve the problem of prescription opioid abuse, including abuse that requires, as a first step, the crushing and pulverization of the dosage form. The art surrounding the branded drug Concerta showed a motivation to make a tablet unusually hard as a means of deterring abuse through crushing and snorting.

In light of this motivation, a skilled artisan would have been led to the prior art teaching the hardness-conferring properties of both hot-melt extrusion and polyethylene oxide. This art included the McGinity Application, which

discloses the hot-melt extrusion of PEO with therapeutic compounds, a process identical, in all crucial respects, to thermoforming. The McGinity Application also discloses many of the '060 Patent's other salient features, including active ingredients with abuse potential, the relevant polymer limitations, and a breaking strength above 500N. These disclosures are supplemented by art describing all of the secondary barriers to abuse recited in Claim 9 of the '060 Patent.

The commercial success of the invention favors Grünenthal, but there was no significant showing of skepticism and acclaim. And even if all the secondary factors favored Grünenthal, the court would nonetheless rule in defendants' favor given their strong showing of obviousness over the prior art.

In the end, the court finds that Grünenthal's invention was obvious when made. Defendants have satisfied their burden and shown, by clear and convincing evidence, that the asserted claims of the '060 Patent are invalid.[21]

C. Roxane's Unclean Hands Defense.

Roxane Laboratories, Inc. asserts unclean hands as an equitable defense to Endo's claims. Roxane argues that Endo, in order to settle an earlier patent infringement case, agreed to not oppose Roxane's launch of its generic

[21] Defendants also argue that the asserted claims of the '060 Patent are invalid for lack of enablement, lack of written description, and indefiniteness. The court disagrees. The patents would teach a skilled artisan how to practice the full scope of the invention without undue experimentation, and would also convey that Grünenthal possessed the entirety of the claimed invention. Thus, the claims are not invalid for lack of enablement and written description. Regarding indefiniteness, the court concludes that each of the asserted claims, including Claim 9 of the '060 Patent, is sufficiently defined to convey the metes and bounds of the invention. Thus, defendants' Section 112 arguments are without merit.

oxymorphone product after a certain date. Roxane claims that after the settlement of the earlier case was complete, Endo took a number of steps to perpetually stall the launch of its generic product. Roxane argues that these actions amount to inequitable conduct which preclude Endo from obtaining an injunction from this court.

The United States courts are courts of law and equity. U.S. Const. art. III § 2. As courts of equity, district courts are closed to those "tainted with inequitableness or bad faith relative to the matter" in which they seek relief. *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). Otherwise, they would risk becoming "abettors of iniquity," giving judicial sanction to those who have acted deceitfully and unfairly to gain an advantage. *See Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933).

In 2009, Roxane filed an abbreviated new drug application to sell a generic version of OPANA®ER. At the time, Endo had three patents in the Orange Book listed as covering the branded drug: the '933 Patent, the '456 Patent, and the '250 Patent. Endo sued Roxane for patent infringement (the "First Action"). However, the litigation was eventually settled pursuant to a Settlement and License Agreement. [redacted]

[redacted]

Two years before Roxane and Endo settled the First Action, Roxane had entered into a supply agreement with Johnson Matthey Inc. ("JMI") whereby JMI agreed to supply Roxane oxymorphone hydrochloride, the active ingredient in Roxane's planned generic product. *See* Supply Agreement Sched. A (DTX-2221). After the Supply Agreement was executed, JMI was awarded a patent, Number 7,851,482, concerning a new, low toxicity formulation of oxymorphone hydrochloride (the "'482 Patent"). [redacted]

[redacted] JMI sold the '482 Patent to Endo pursuant to a Patent Purchase Agreement. *See* Patent Purchase Agreement (DTX-2209).

[redacted]

In 2012, Endo was awarded two new patents, the '122 and '216 patents, which cover its branded-oxymorphone product. In May of 2013, Endo filed the instant lawsuit against Roxane for patent infringement, asserting both its newly won patents (the '122 and '216 Patents) and the patent it had purchased from Johnson Matthey (the '482 Patent). *See* Compl. ¶¶ 18–25. As trial on these

patents approached, Endo stopped asserting the '482 Patent. Thus, only the '122 and '216 patents were litigated at trial. Endo has also filed a third lawsuit against Roxane in the District of Delaware, asserting infringement of another patent.

Having reviewed Endo and Roxane's evidence *in camera*, the court concludes that Endo has not acted inequitably in this case. Roxane's unclean hands defense is less complicated than it seems, and amounts to this: [redacted] but (2) after the settlement was finalized, Endo took a number of steps, [redacted] and filing two new lawsuits, in order to perpetually prevent Roxane from entering the market.

[redacted]

[redacted]

The court infers no inequitable motive surrounding Endo's purchase of the '482 Patent from JMI. [redacted] Finally, Endo stopped asserting the '482 Patent in this case. Thus, the court see no relationship between Endo and JMI's actions and the matters asserted at trial.

Finally, the court sees no inequity arising from Endo's assertive litigation strategy. At trial, Endo's witnesses explained that OPANA®ER is Endo's flagship product. The entry of generic competition represents an existential threat to the company. To confront this, Endo is clearly entitled to assert its patents. Congress, of course, has created mechanisms for generic manufacturers, like

Roxane, to challenge those patents. But generic manufacturers are sophisticated entities, and upon settling litigation regarding one patent are perfectly capable of insisting that the settlement cover future patent issuances. There is nothing inequitable about a company, like Endo, asserting wholly different patents when they issue or are otherwise acquired.

Conclusion

For the reasons given above, the court concludes that defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid. The court concludes that defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid.

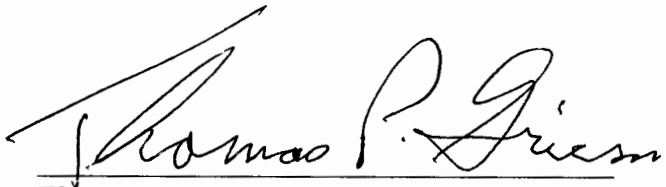
The court enters judgment in Endo's favor and enjoins defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents. Moreover, the court orders that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents. *See* 35 U.S.C. § 271(e)(4).

Because defendant Actavis is already on the market with its generic product, it shall have sixty days from the date of this decision to comply. The court reserves decision on whether to award additional relief, including damages against defendant Actavis, pending further briefing from the parties.

Endo's recently filed motion to strike Amneal's obviousness defense in case number 12-CV-8115 is moot. The clerk of court is directed to resolve all pending motions in the above captioned cases.

SO ORDERED.

Dated: New York, New York
August 14, 2015



Thomas P. Griesa
U.S. District Judge